Research for Development

Carlo Boccato
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Medical Devices

Improving Health Care Through a Multidisciplinary Approach

Springer

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Foreword

The development and application of medical devices has a long history. Some years ago, a 3000-year-old wooden toe prosthesis was found attached to a female mummy in an ancient Egyptian grave site [1]. It is one of the oldest prosthetic devices in the world's history and shows both the engineering skills of our ancient ancestors and their medical experience. Further examination of the prosthesis has revealed details about the time from which it came. With technologies like modern microscopy, X-rays and computer imaging, a team of researchers were able to determine the materials and methods used to make the prosthetic. They found that the wooden toe was refitted several times. Based on the meticulous construction of the ancient prosthesis, the researchers determined the wearer, a priest's daughter, who wanted the toe to look natural and be comfortable to wear. About 2,500 years later, the famous astronomer Tycho Brahe (1546–1601) profited from a spare part, when he received a golden artificial nose after having lost his nose in an affair of honour at my hometown's University of Rostock. Some years earlier in 1518 AC, the famous German chevalier Goetz von Berlichingen (1480–1562) and protagonist of the German Peasants war in the beginning of the sixteenth century received an iron artificial hand and could thus continue fighting with the help of such a prosthesis. These examples illustrate that the history of medical devices including artificial body spare parts can be rewritten in such a way as engraved in the building of the Department of Justice in Washington: "What is past is prologue!"

Medical devices save indisputably lives. Recent years have seen an enormous push in the development of both new medical devices and medicinal drugs. This is certainly based on an increased knowledge combined with managerial competence and a pressure originating from demographic changes. The increase in the number of elderly people and the related loss of body functions further stimulates research and application of sophisticated devices with "performance" as a magic word. Performance of medical devices is closely related to their approval which is a prerequisite of sales and marketing. Medical devices must further reach the affected patient, which explains why logistics, health insurances and financial budgets also play a major role, both in the western hemisphere and in the so-called Third World. The

development of medical device is costly, and thus a return of investment for manufacturers and healthcare providers cannot be neglected. The search for new ways of efficient financing all over the world is, therefore, a challenge for the current medical device technology. Taken together all these influencing factors can be integrated through a "*Systems Approach*" [2]. A systems approach in medical device technology bases on the combined efforts of dedicated engineers, physicians and managers for both well performing devices and therapies and to achieve optimal cures for a high quality of life of patients. To my great pleasure, and more than 30 years after the introduction of this keyword, this book perfectly advances the understanding, development and promotion of medical device technology as a "systems approach".

This book provides to my knowledge the first comprehensive and well-documented book in the field of medical device technology by providing engineering, economic and medical rationales for the development and use of medical devices. The collaborative work of the editors and authors brings to you a book which represents indisputably a perfect overview about the actions which determine the conditions for providing and sustaining medical devices. I also welcome in this book the description of tasks of individual stakeholders, not to forget financial aspects and the provision of medical devices in emerging third world countries. I hope that this book will serve as a vehicle for a better understanding of the background and problems of medical device technology and that interested readers profit from its wide dissemination.

References

1. Nerlich A, Zink A, Szeimies U, Hagedorn H (2000) Ancient Egyptian prosthesis of the big toe. Lancet 356(9248):2176–2179
2. Klinkmann H, Falkenhagen D, Stefoni S, Bonomini V (1989) Biocompatibility, a Systems Approach. Contrib Nephrol 70:213–226

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Horst Klinkmann

Introduction

Why to write (and possibly read) a book entitled *Medical Devices: Improving Health Care Through a Multidisciplinary Approach*?

It is almost a platitude to say that medical devices—with different levels of complexity—are pervasive in today's medical treatments. The topic has been indeed treated by a series of competent authors. This book will outline that a multidisciplinary approach to be applied to the use of medical devices has undoubtable immediate benefits to the patient's clinical outcome. In addition, this approach can improve the value created for the healthcare system to benefit patients and communities.

In addition, current demographic changes, such as the ageing of the population, and the increase of chronic diseases leading to long-lasting and repeated treatments, create an additional challenge to the sustainability of the healthcare systems.

The use of technology and tools in medicine has a long history. In the industrialised world, a huge number of different devices and equipment have been introduced to the medical field to support diagnosis, therapy and rehabilitation. In recent years, this trend has provoked the development of new devices. When considering the current concept of personalised medicine, new ideas and models are urgently needed.

The increasing use of highly sophisticated medical devices, such as MRI, PET-SPECT, and artificial organs, may increase the cost for treatment. This may also be due to the raised therapeutic expectations which will also lead to a higher demand for reimbursement by the community.

For the above reasons, the quest for value and improvement of efficiency in health care has become a hot topic in this field. The complexity of a technology-based healthcare system, however, requires looking at it from different perspectives. This means to consider a *systems' approach* for the application of medical devices, depending not only on the condition of the patient. This approach also involves medical science, environmental conditions, engineering, organisational, normative and economic aspects.

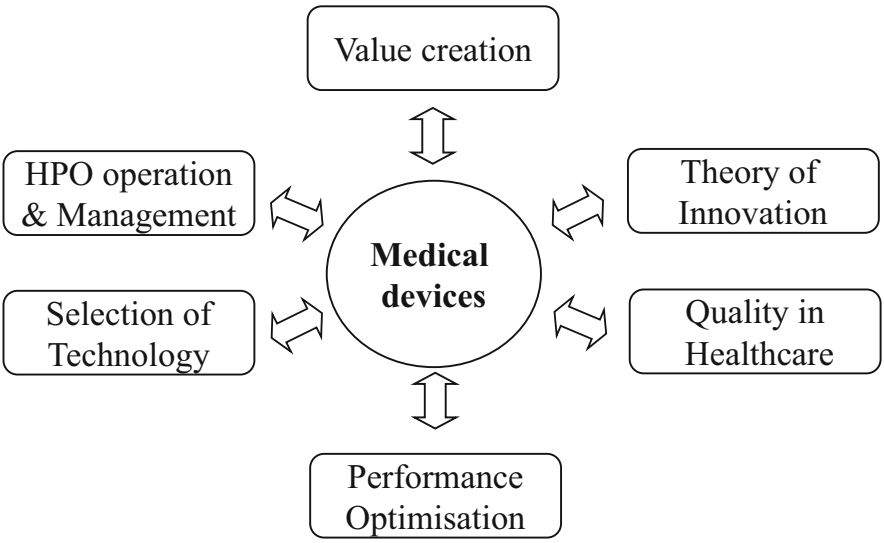

Fig. 1 Topical clusters in relation to medical devices, which will be addressed in the following chapters (HPO—Healthcare Provider Organisation)

This multi-perspective view is the objective of this book. It will show that a *consistent* and *multidisciplinary* management of medical devices offers an important support for healthcare institutions. The subject of medical devices goes together with at least six topical clusters, as represented in Fig. 1.

These clusters underline the multidisciplinary nature of the application of medical devices and are at the basis of the questions arising in the everyday life of operators and decision makers:

- What is the meaning of *value* in health care?
- How can the healthcare system and organisations pursue the *value, quality and sustainability of care*?
- How to decide about the best applicable *medical technology*?
- How to control the *quality and safety* of the application of medical technology?
- How can a Healthcare Provider Organisation (HPO) optimise its *performance* with the use of medical devices and equipment?
- What is the role of *innovation* in health care (medical devices)?

In the following, this book will provide possible answers to the above questions. They are based on the experience gained in academia, in both research and healthcare institutions as well as in industry. This book further aims to support decision makers (engineers, caregivers and administrators) in deciding on operational and strategic movements when dealing with complex medical devices. We hope that this work can make a contribution to the quest for the increasing quality and efficiency in health care for the benefit of the patient and the community.

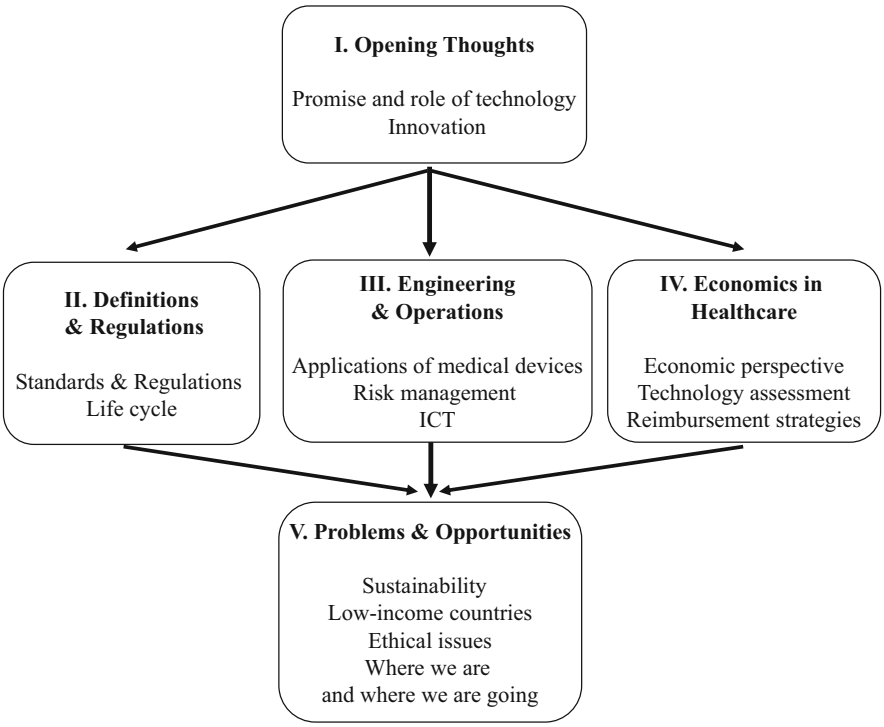

Fig. 2 Structure of the book showing the roadmap to guide the reader along a multidisciplinary tour (ICT—Information and Communication Technology)

Figure 2 shows the roadmap followed in the book to guide the reader along this multidisciplinary tour.

Part I provides an introduction of the overall topic presenting the author's considerations on what are the potential improvements that medical devices and equipment can bring to health care (Chap. 1), which is also seen in an approach to individualised therapies (Chap. 2). But in our society *technology* is almost a synonym of *innovation*, this is why we added (Chap. 3) an examination of the innovation theory in medical technology.

Part II clarifies some basic definitions and provides an overview of the standards and regulations applied in the field (Chap. 4) and presents (Chap. 5) the typical lifecycle of a medical device to show what are the main issues to consider when dealing with these devices, always keeping the effectiveness of the therapy and the patients' (and operators') safety in mind. In this chapter the development of a cardiac arrhythmia monitor is presented as a case study.

Part III describes some of the important points that healthcare institutions should consider when operating the medical devices. Chapter 6 analyses the impact of medical devices in a generic healthcare provider organisation and gives some

examples based on the haemodialysis treatment. The problems connected to the patient's security due to the extensive use of ICT are considered in Chap. 7.

Part IV contains information about economics and value in health care. Chapter 8 deals with economic perspectives of medical devices. The concept of value and the economic assessment of medical technology are treated in Chap. 9. Finally, reimbursement systems and pay-for-performance are discussed in Chap. 10.

Part V deals with the problems and opportunities that come with the wide application of medical devices. Chapter 11 mainly addresses the issue of healthcare sustainability. Opportunities and problems related to the application of new technologies in low- and middle-income countries are considered in Chap. 12.

Ethical aspects connected to the use of medical devices are considered in Chap. 13.

And finally, in Chap. 14 the authors provide closing remarks and discuss a prognostic view of the possible future developments of medical therapy.

Carlo Boccato
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Abbreviations

3Rs	Reliability, Reproducibility and (Re)traceability
AAMI	Association for the Advancement of Medical Instrumentation (in USA)
ACE	Angiotensin-converting enzyme
ADME	Absorption, distribution, metabolism, elimination
AIFA	Agenzia Italiana del Farmaco (Italian Agency for Pharmaceutical Drugs)
AIMD	Active Implantable Medical Devices (in Europe)
AMA	Authorisation to the Market Admission
ANSI	American National Standards Institute
ASTM	American Society for Testing and Materials
ATMP	Advanced therapeutical medicinal products
BCIs	Brain-Computer Interfaces
BLA	Biologics License Application (in USA)
BOM	Bill of Materials
BPA	Bisphenol A
BPS	Bisphenol S
CAPA	Corrective and preventive action
CAS	Complex adaptive system
CBA	Cost-benefit analysis
CDC	Centers for Disease Control—in USA
CDRH	Center for Device and Radiological Health—in USA
CDVC	Care delivery value chain
CE	Conformité Européenne
CEA	Cost-effectiveness analysis
CEN	Comité Européen de Normalisation—European Committee for Standardization
CENELEC	Comité Européen de Normalisation Electrotechnique—European Committee for Electrotechnical Standardization
CGM	Continuous glucose monitoring

CMA	Cost minimization analysis
CoI	Cost-of-illness
CSIRT	Computer Security Incident Response Team
CUA	Cost-utility analysis
DEHP	Bis(2-ethylhexyl)-phthalate
DMSO	Dimethylsulfoxide
DPO	Data Protection Officer
DRG	Diagnosis-related groups
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EMR	Electronic medical records
ENISA	European Union Agency for Cybersecurity
EP	Essential Principles—Japan
ePHI	Electronic protected health information
EQ-5D-3L	The Euro Quality of Life—5 Dimensions—3 Levels
ETO	Ethylene-oxide
EU	European Union
EUDAMED	European Database on Medical Devices
EUnetHTA	European Network for Health Technology Assessment
FDA	Food and Drug Administration (in USA)
FHIR	Fast Healthcare Interoperability Resources
GCP	Good clinical practice
GDP	Gross domestic product
GDPR	General Data Protection Regulation
GHTF	Global Harmonization Task Force
GLP	Good laboratory practice
GMP	Good manufacturing practice
GNI	Gross national income
GP	General practitioner
GPC	Gel permeation chromatography
GSPRs	General safety and performance requirements
HBHTA	Hospital-based HTA
HCS	Healthcare system
HD	Haemodialysis
HDE	Humanitarian Use Exemption in USA
HDO	Health care delivery organisation
HHS	U.S. Department of Health and Human Services
HIPAA	Health Information Portability and Accountability Act
HNWI	High-net-worth individual
HPO	Healthcare provider organisation
HS	Horizon scanning
HTA	Health technology assessment

ICD	Implantable cardioverter defibrillator
ICT	Information and communication technology
ICUR	Incremental cost-utility ratio
IEC	International Electrotechnical Commission
IfU	Instructions for use
IMDR	International Medical Device Regulators Forum
IMPAQHTA	IMPlementation of a quick hospital-based HTA
INAHTA	The International Network of Agencies for Health Technology Assessment
IP	Intellectual property
IP	Internal protection
ISO	International Organization for Standardization
IT	Information technology
IVDR	*In-Vitro* Diagnostic Devices Regulation (in EU)
JAMA	Journal of the American Medical Association
JISC	Japanese Industrial Standards Committee
KPI	Key performance indicator
LOC	Lab-on-a-chip
LVADs	Left ventricular assist devices
MCDA	Multi-criteria decision analysis
MD	Medical device
MDD	European Medical Device Directive
MDM	Medical device manufacturer
MDR	European Medical Device Regulation
MEDDEV	European Medical Device Guidance document
MHLW	Japan's Ministry of Health, Labor and Welfare
MONDO	Monitoring Dialysis Outcomes
MRI	Magnetic resonance imaging
MW	Molecular weight
NCD	Non-communicable diseases
NGO	Non-governmental organisation
NHS	National Health Service (UK)
NICE	National Institute for Health and Care Excellence (UK)
NIS	Network and information security
NPO	Non-profit organisation
NPV	Net present value
NUB	Untersuchungs- und Behandlungsmethoden , meaning new methods of diagnosis and treatment
OECD	Organization for Economic Cooperation and Development
p.c.	Per capita
P4P	Pay for performance
PAL	Pharmaceutical Affairs Law (in Japan)
PC	Polycarbonate
PCB	Printed circuit board

PDP	Product Development Protocol (in USA)
PEG 400	Polyethyleneglycol
PHD	Pharmaceutical drug
PK	Pharmacokinetics
PLC	Product life cycle
PM	Pacemaker
PM	Particulate matter
PMA	Pre-market approval
PMCF	Post-market clinical follow-up
PMD Act	Pharmaceuticals and Medical Devices Act (in Japan)
PMDA	Pharmaceutical and Medical Device Agency (in Japan)
PMMA	Poly-methyl-methacrylate
PMPs	Platelet-derived microparticles
PMS	Post-market surveillance
PMSR	PMS reports
POC	Point-of-care
PP	Polypropylene
PPE	Personal protective equipment
PSu	Polysulfone
PSUR	Periodic Safety Update Report
PUR	Polyurethane
QMS	Quality management system
QOF	Quality and Outcomes Framework
QoL	Quality of life
R&D	Research and development
REA	Rapid Relative Effectiveness Assessment
REACH	Registration, Evaluation, Authorization and Restriction of Chemicals (in Europe)
RoHS	Reduction of Hazardous Substances
ROI	Return on investment
SHI	Statutory health insurance
SOP	Standard operating procedures
SPRs	General Safety and Performance Requirements (in EU)
SROI	Social return on investment
STED	Summary Technical Documentation in Japan
SUD	Single use device
TAH	Total artificial heart
TAM	Technology acceptance model
TAT	Thrombin-antithrombin III complex
TCO	Total cost of ownership
UDI	Unique device identification
UHC	Universal healthcare
USP	United States Pharmacopoeia
UTAUT	Unified theory of acceptance and use of technology

VAS	Visual analogue scale
VBH	Value-based healthcare
WHO	World Health Organization
WTP	Willingness-to-pay

Part I
Opening Thoughts

Chapter 1
The Medical Devices Promise to the Healthcare System

Carlo Boccato, Sergio Cerutti, and Joerg Vienken

Abstract The chapter analyses possible contributions offered by medical devices technology in order to tackle the troubles affecting healthcare services worldwide. These issues affect the efficacy and efficiency of all healthcare systems, finally undermining their very sustainability. The most evident problems, at least in the affluent part of the world, are rising cost, mainly due to demographic changes and the increase of non-transmissible chronic diseases. In addition, the lack of adequate healthcare for the lower-income part of the society is evident and unacceptable.

The chapter will focus on the creation of value for the patients and other stakeholders starting from the care delivery value chain and will underline the contribution of the technology to improve the different healing steps.

A special consideration will be given to the need of a *consistent* and *multidisciplinary* approach including all the different components of the healthcare system from technology to infrastructure to human resources and the involved stakeholders.

Introduction

The global healthcare system[1] suffers from many issues that undermine its effectiveness and long-term sustainability.

[1] Following the definition of the World Health Organization, a health system "consists of all organizations, people and actions whose primary intent is to promote, restore or maintain health". Its goals are "improving health and health equity in ways that are responsive, financially fair, and make the best, or most efficient, use of available resources" [15].

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The most evident concerns are rising costs mainly due to the increase of the elderly population, its higher morbidity and the increase of non-transmissible chronic diseases. These causes are more evident in the most affluent societies, but are now extending also to lower-income countries, as underlined by a WHO report [1].

As will be detailed in the following, healthcare systems are not always able to provide the adequate level of care to the vast majority of people worldwide due to increased expenditure in labour and medication. Moreover, we often observe the lack of minimal level of care in low-income countries and for lower-income people even in affluent societies.

Many authors identify the key point to solve these systems' weaknesses. They propose the healthcare systems to become more focused on the delivery of value for the patients and the community they serve.

This chapter will deal with first observations that a *consistent and multidisciplinary* use of medical devices can be instrumental to find solutions for the problems of healthcare systems.

1.1 The Medical Devices Technology: A Preliminary Definition

According to the Medical Device Regulation 2017/745 of the European Union (EU MDR), a *medical device* can be defined as any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease[2] [2]).

According to this definition, the term *medical device* covers a wide range of products, spanning from a simple wooden-made tongue depressor to a hospital bed to a complex MRI or X-ray equipment.

With the present development of the technology, the expression *medical device* includes also the group of contrivances that, even if not originally designed for medical application, are now used for healthcare purposes, perhaps with auxiliary functions. In fact, the dedicated (and possibly wearable) sensors, supplemented by software and functions embedded in smartphone and smartwatch, are a further promising source of innovation and diagnostic support. Devices based on artificial intelligence (AI) and big data analyses systems should also be considered in this group.

[2]The quoted definition from EU MDR has been shortened to improve the readability. A substantially similar definition is given by WHO. More precise and detailed designation, together with the relevant implications, can be found in Chap. 4 of the present book.

It must be ensured that the collected data have a real medical meaning and can be used for diagnosis, prevention and therapy. For this reason, it is mandatory to apply here all the regulations as done for the "traditional" medical devices.

1.2 The Main Challenge

It seems that the destiny of every complex system, such as a society or an organization, is to be challenged by considerations on effectiveness, efficiency and sustainability (see Chap. 11 for more details) [3–5]. The solution to this problem usually requires a committed change in perspective by all stakeholders. This also holds true for the healthcare systems today.

With respect to the recent past, we experience the availability of an incredible amount of new and encouraging powerful tools and technologies for diagnosis and for successful therapies. We are also confronted with a complex and difficult scenario, characterized by:

- Ageing of the population, at least in the wealthier countries, that increases the need to treat chronic illnesses with the consequent upsurge of related cost.
- Explosion of the cost, especially in the affluent part of the world. This might also be provoked by the increased expectations stimulated by the successful progress of healthcare technology [4].
- Need to ensure the adequate health assistance to a wider part of the population in lower-income countries and to the less wealthy group of the population in affluent societies.
- Reduced marginal returns of healthcare expenditure, e.g. in terms of acquired healthy life years versus the total expenditure. This seems to be a "law" for all the complex organizations. This is especially perceived in the countries where the total expenditure is high [3–5].

The reduction of the marginal return for healthcare expenditure is illustrated by the diagram in Fig. 1.1 [6].

This trend dramatically shows that in all countries belonging to the Organization for Economic Co-operation and Development (OECD), the increase of expenditure in healthcare does not yield a linear improvement in the healthy life expectancy at birth.

A similar behaviour can be found when considering the expected improvement of the QALY over the expenditure.

QALY (Quality Adjusted Life Years) is a measure of the burden of disease. The concept is to weight the years of life lived with a defined quality of the life. One QALY is equal to 1 year in perfect health. The presence of any sort of disability assigns a weight less than one. The basis for the assessment of QALY is a generally accepted questionnaire.

A more detailed discussion of this aspect can be found in Chap. 11.

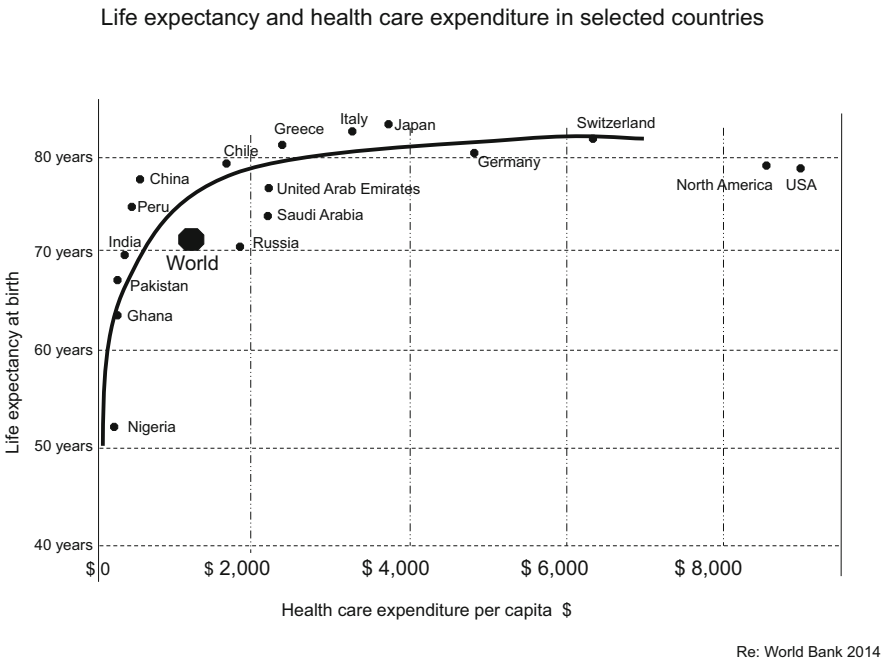

Fig. 1.1 The increasing expenditure in healthcare does not result in a proportional increase in life expectancy. This suggests a reducing return in the healthcare investments. (Modified from [6])

1.3 A Possible Answer

The majority of authors, including the group of experts at World Economic Forum (WEF) 2020, agree that the change of the present paradigm of healthcare systems seem to be the only real solution to afford the above-mentioned challenges [5]. This approach promises to be the most powerful and sustainable one in the long term, especially if compared with the plain cost-cutting exercise, which is often much appreciated by the policymakers.

Basic research, best practices dissemination and a value-based reimbursement are among the most powerful tools to achieve this paradigm change together with a patient-centric approach. This can bring value in the system and increase the return of spent resources. The creation of a patient-centred healthcare system requires to move from a *quantity-based* delivery of services to a *value-based* approach and evaluation [7–10].

We assume that a major contribution to these concepts can be provided by medical devices.

This approach suggests that the therapies, or the medical acts in general, should be chosen (and possibly reimbursed) not (only) on the basis of their quantity, but

(mostly) on the value they can create for the health and well-being of the patients (see also Chap. 10 of this book).

According to Kaplan and Porter [9], the value in healthcare should be measured in terms of the patient achieved outcomes according to the money spent.

This can be summarized as:

$$\text{Value} = \frac{\text{Health outcome of the patient}}{\text{Costs for the delivery of the outcome}}$$

The starting point is to correctly define the health outcome of patients. Too often this is intended just as the plain delivery of services, with the assumption, that more (delivered) services is equal to more (delivered) value. A model developed by M. Porter et al. [8–12] suggests instead to focus on the real health and life quality improvements achieved by the patient. This includes a possible patient discomfort experienced during the treatment and the sustainability of the reached health status.

These authors underline the need to concentrate on the overall value created for the patient, rather than on parameters that are only giving a partial view of the caring activity. The proposed model indicates three tiers for the assessment of what has a real value for the patient. This hierarchy of achievements includes:

- Patient's achieved health status or maintained in case of degenerative/chronic illness.
- Process of healing including the possible discomfort created by or connected to the therapy.
- Process of recovery (time for achieving the best possible health status and possible suffered discomfort).
- Sustainability of the achieved health status including the resulting quality of life (QoL) and need for possible re-interventions.

Each of the above tiers may be subdivided in additional subcategories, according to the specific pathology and treatment strategy.

The complexity of medical treatment should also consider a set of many competing outcomes, e.g. near-term versus long-term functionality. These must be weighted to achieve the best compromise, also in light of the patient's individual preference. For the purpose of the present discussion, we can avoid to go into further detail.

The creation of value for the patient is accomplished through different steps that can be summarized, according to the above authors, with the Care Delivery Value Chain (CDVC). This chain shows the different activities undertaken at the different stages of an illness, from prevention, to diagnosis, treatment and rehabilitation. The detailed steps should be further specified depending on the pathology under consideration.

Table 1.1 shows the main steps to be undertaken for the creation of value in healthcare. This generic chart should be enriched with more details according to the pathology, illness status and healthcare insurance.

The relevant activities can be categorized in two main areas:

Table 1.1 Generic CDVC showing the different steps for the creation of value for the patient

Informing	What the patient needs to know					
Measuring	What data need to be collected					
Accessing	Where do patient's care take place					
Delivering care	Monitoring Preventing	Diagnosis	Preparing	Intervening	Recovering Rehabilitation	Monitoring Managing

Reduced and adapted from Porter [8]

- Supporting activities such as informing, measuring and accessing.
- Primary activities directly devoted to the delivery of care.

Again, making reference to a non-specific treatment model, the contribution of the medical devices to each of these activities can be summarized in Table 1.2.

The achievement of the value for the patient should be observed and monitored at each step of the value chain.

As shown by WEF in 2020 [5] and by E. Topol in 2012 [13], the transition to a new type of healthcare is controlled by the intense application of new technologies. In addition, many techniques inherited from other fields of engineering can provide an important support.

This is the case of the application of highly sophisticated prosthetic devices and artificial body parts and organs, robotic tools, advanced imaging techniques, dedicated non-invasive and invasive sensors for physiological parameters, algorithms and computing power.

Table 1.3 and map in Fig. 1.2 give another, perhaps more comprehensive, view of the possible contribution of the medical devices to the change of the healthcare paradigms.

The *super convergence*[3] [13] of all these instruments paves the way towards the new medicine, but also helps to improve the present praxis and allows for an important cost saving.

One possible example is the continuous collection of important parameters obtained with non-invasive and invasive sensors or with devices autonomously operated by the patient.

This procedure supports all phases of the care delivery chain, especially if the collected data can be shared among all the different caregivers at various stages of the caring process, possibly through a well-designed IT-infrastructure.

The power of internet in improving the literacy of the patients and the availability of "consumer" devices should not be underestimated. It allows a sort of "informative self-monitoring" of the patient. Such tools can support the decision-making of the people for an early referral to caregivers in case of possible pathologies. In this way it is possible to achieve a healthier way of life at an earlier stage or a better compliance with the prescribed therapy.

An important *caveat* at this point is to ensure the correctness and precision of the information made available to the patients (usually via internet) and the reliability of consumer devices.

Misleading communication can give rise of the generation of wrong expectations for applicable therapies among sick people. This is an area to be strictly monitored and controlled by medical authorities, regulatory institutions and policymakers.

[3] The term has been used by E. Topol [13] to make reference to the contemporary availability and ubiquity of the digital technologies (including smartphones) that may support, e.g. the self-monitoring of vital parameters, the social networking, the pervasive connectivity, the imaging capability and the powerful data processing tools.

Table 1.2 Generic CDVC showing the contribution of the medical device

Informing	Patient's literacy, internet, group communications and education . . .					
Measuring	Wearable sensors, self-monitoring, . . .					
Accessing	IT systems, telemedicine, . . .					
Delivering care	Monitor Prevent	Diagnosis	Preparing	Intervening	Recovering Rehabilitation	Monitor Manage
	Monitoring-Self-monitoring tools	*Diagnostic tools*	*Diagnostic tools*	*Diagnostic tools*	*Monitoring-Self-monitoring tools*	*Monitoring-Self-monitoring tools*
	Support for compliance to therapy	*AI diagnosis supporting tools*		*Robotics tools*	*Support for compliance to therapy*	*Support for compliance to therapy*
	IT for clinical record	*IT for clinical record*	*IT for clinical record*	*IT for clinical record*	*IT for clinical record*	*IT for clinical record*

Adapted from M. Porter [8]. *CDVC* Care Delivery Value Chain, *IT* Information Technology, *AI* Artificial Intelligence

Table 1.3 How the medical devices can contribute to healthcare improvement (IoMT—Internet of Medical Things, AI—Artificial Intelligence)

Devices and tools	Supporting methods and strategies	Objectives to be achieved
• IoMT • Registries • Big data and AI • IT tools for interactive education • Biosensors • Telemedicine • Precise imaging systems • Effective artificial organs • Advanced prosthetic systems	• Precision medicine • Healthcare outside the clinic • Sharing patient's data/clinical history • Automatic support to diagnosis • Remote medical consultation • Focus on patient's ecosystems	• Short- and long-term improvement of diagnosis and therapy • Reduction of diagnostic errors • Prevention of under/overtreatment • Preventive medicine • Seamless continuous care • High level of care in remote areas • Reduce/optimize the costs of care

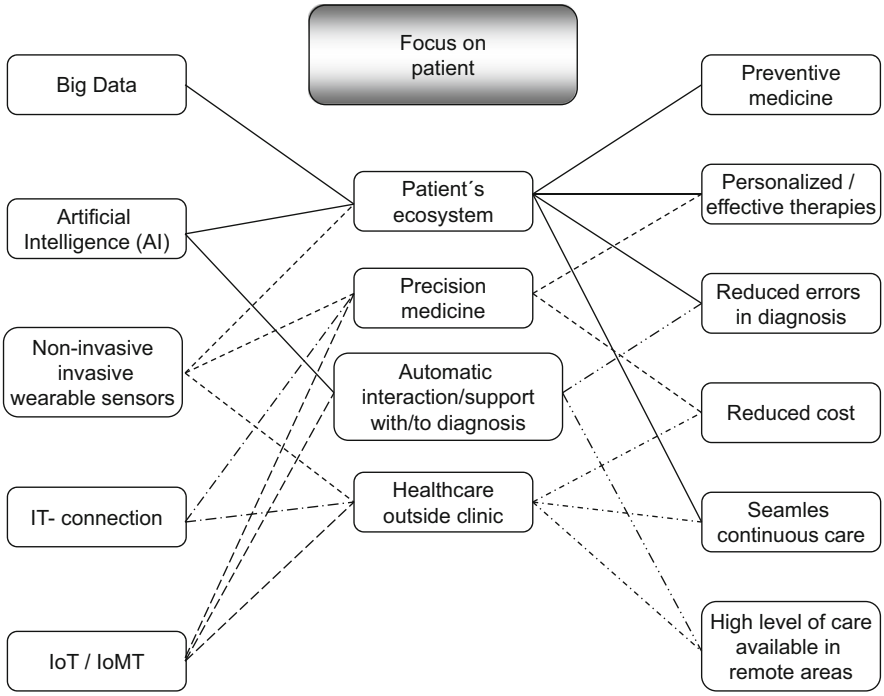

Fig. 1.2 Contributions of the medical devices to the healthcare paradigm change. (*IoT* Internet of Things, *IoMT* Internet of Medical Things, *IT* Information Technology)

In addition to the items listed in Fig. 1.2, it is important to remember the need for the availability of low-cost and hi-quality "simple devices", like syringes, personal protective equipment (PPE), disinfection devices, face masks or simple medication disposables. The availability of these medical devices with acceptable quality and reliability also in remote areas or in low-income countries might not always be granted. These are important means to improve the overall health status of the population by e.g. avoiding the spread of infections, allowing for effective vaccination campaigns and reducing mortality [14, 15].

The medical device technology as shown in Fig. 1.2 also influences the social aspects of healthcare mainly through:

- Moving the patients towards "self-care" and more autonomous implementation of therapies.
- Influencing positively the communication between patients and professional caregivers implementing a deeper and more precise flow of information about pathologies and possible therapies [4].

1.4 The System Thinking

The successful clinical application of any medical device, especially in the case of complex equipment, needs to consider several dimensions and a fully multidisciplinary approach. This holds also true for the subsequent successful outcome of the medical act.

As reminded by WHO [16], system thinking is an essential approach for success in designing and operating the healthcare systems and healthcare provider institutions.

Figure 1.3 summarizes the different aspects and actions involved in the successful application of the medical technology, of which the medical devices represent a larger part.

All medical acts suffer from the ambiguity between a remedy and a potential creation of damage [17]. For this reason, we must operate the trade-off between benefits and risks, even in the clinical application of medical devices. This aspect is becoming more and more significant in light of the increasing complexity of devices and systems which are currently available on the market. The topic is involving all stakeholders, i.e. engineers, notified bodies (for normative and regulation requirements) as well as caregivers. The compliance to these prerequisites ensures that the devices put on the market are *fit for purpose*, meaning that they deliver the claimed benefits and are, at the same time, safe for the patients and operators.

The delivered benefits and the sustained cost are also important area of trade-off. The cost issue, even if perhaps not considered in the historical medical literature, is of utmost importance. This is due to the present complexity of many devices themselves and to the increasing healthcare demand.

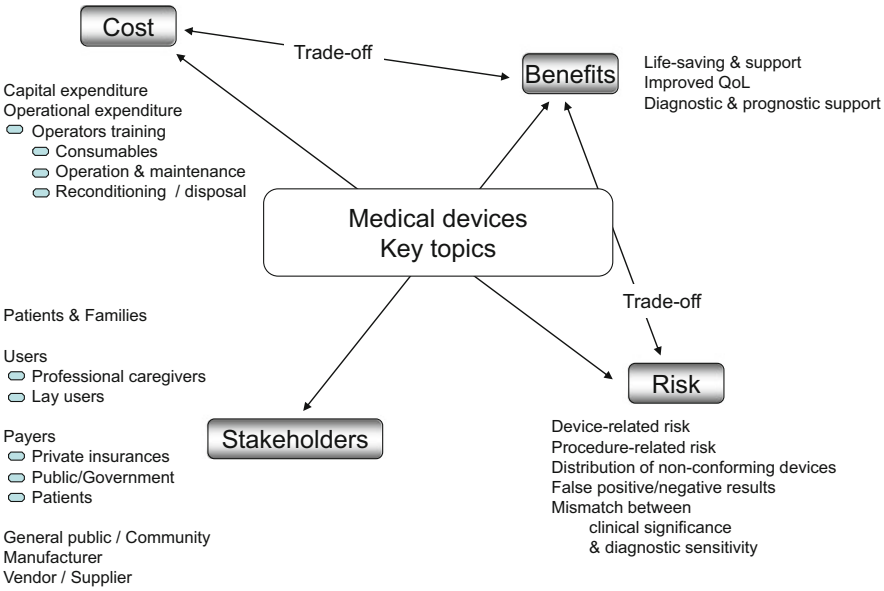

Fig. 1.3 Key trade-offs and impact factors that are involved in medical device application

The costs evaluation includes many aspects, basically the capital and operational costs. They must be subject to careful consideration by decision makers, such as in politics and in healthcare institutions (see also Chap. 6).

Another important area of interest is relevant to the different stakeholders involved in the selection and use of the devices. This group acts like a business chain and spans from manufacturers, vendors, decision makers and operators and finally patients.

The healthcare is a very specific branch of human activities, dealing with human beings and with their physical and mental health with the final goal to improve quality of life. The healthcare technology involves not only the healthcare professionals and the patient under treatment but also the relatives and people in contact with her/him. This group includes a potential lay user of medical devices and spreads up to the whole community.

Political decisions are also deeply affected, especially concerning the economic affordability and sustainability of the technological choices. Political decisions and market dynamics also influence and promote the development and the adoption of innovative solutions (see also Chap. 3). In addition, it is important to consider the implications of new and complex technologies on the consolidated healthcare system. The successful outcome of the healthcare act is influenced by many actors and resources as summarized in Fig. 1.4 [4, 16].

All the aspects illustrated in Fig. 1.4 influence the correct use of the medical devices and are affecting the successful implementation of the therapy.

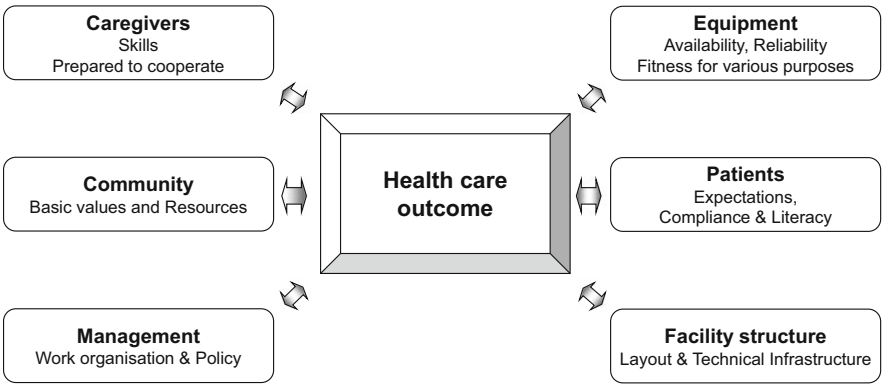

Fig. 1.4 The implications of medical technology on the healthcare system

A general but not exhaustive list includes:

- The devices should be reliable, safe, effective and implemented according to standards and directives.
- The caregivers (either professional or not) should be trained and open to use the technology.
- The community should be willing to accept the use of these device and ready to allocate the required resources for their availability and full accessibility.
- The management (also at political level) should operate for the accessibility and affordability of the devices and provide resources and required work organization.
- The healthcare institutions (inside or outside the traditional hospitals) should prepare their physical infrastructures for the effective use of these devices.
- The patients and lay caregivers must have the adequate literacy for the use of the devices. This is part of the education on the compliance with therapies.

The main message behind the above considerations is that the benefits coming from the use of medical devices necessarily require a genuine multidisciplinary approach. This involves the people's mindset and culture, the infrastructure design and management as well as the political choices.

Conclusion

From the above discussion, it is possible to summarize the contribution of medical devices to problems presently affecting the healthcare system:

- Availability of monitoring tools since the early inception of the illness to allow prevention and early referral. This allows a better health status for the patients and avoid/reduce the cost for the treatment of a heavier illness status.
- Availability of devices that may help the (potential) patient either in the prevention phase or in the recovery phase (post treatment, e.g. surgery). This holds true for monitoring or self-monitoring tools as well as for devices that can support the

patients/caregivers in maintaining the required compliance to the prescribed therapies.
- Availability of devices supporting the patients in acquiring the best possible level of autonomy.

All these can help the healthcare environment to increase the value for the patients, seen as a better outcome with a containment of the cost in a socially acceptable way.

Take Home Message
- The ageing of the population, the spread of chronic diseases and the reduction of the investment return in healthcare are undermining the long-term sustainability of the healthcare systems worldwide. In addition, the lower-income part of the population may still lack the adequate level of care.
- The solution to the above issues requires a change in the present healthcare paradigm.
- The use of medical devices, characterized by different level of complexity, can have a positive impact on the improvement of each step of the care delivery value chain and in the needed change of healthcare paradigm.
- A system approach, to consider all the involved aspects, from technical knowledge, to personnel management to economics and innovation is a key factor to ensure the full exploitation of the medical devices potential.

References

1. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases. Accessed 28 June 2021
2. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
3. Tainter J (1988) The collapse of complex societies. Cambridge University Press, Cambridge
4. Webster A (2007) Health, technology and society. Palgrave Macmillan, Basingstoke and New York
5. World Economic Forum (2020) The new health paradigm. https://www.weforum.org/videos/the-new-health-paradigm
6. World Bank (2019) Life expectancy vs. health expenditure 1970 to 2015. https://ourworldindata.org/grapher/life-expectancy-vs-health-expenditure
7. Porter ME, Lee TH (2013) The strategy that will fix health care. Harv Bus Rev 91(10):50–70
8. Porter ME (2010) What is value in health care? N Engl J Med 363:26
9. Kaplan RS, Porter ME (2011) How to solve the cost crisis in health care. Harv Bus Rev 89(9):47–64
10. Porter ME, Lee TH (2015) Why strategy matters now. N Engl J Med 372:18
11. Porter ME, Teisberg EO (2006) Redefining health care. Harvard Business School Publishing, Boston

12. Porter ME (1985) Competitive advantage creating and sustaining superior performance. The Free Press A Division of Macmillan, Inc., New York
13. Topol E (2012) The creative destruction of medicine. Basic Books, New York
14. WHO list of priority and medical devices. https://www.who.int/medicaldevices/priority/en
15. World Health Organization (2007) Everybody's business: Strengthening Health systems to improve health outcomes: Framework for action. WHO, Geneva
16. De Savigny D, Adam T (eds) (2009) Systems thinking for health systems strengthening. World Health Organization, Geneva
17. Curi U (2017) Le parole della cura - Medicina e filosofia. Raffaello Cortina Milano (text in Italian)

Chapter 2
The Role of the Engineer and Technology in Healthcare

Joerg Vienken

Abstract The engineer in charge with developing, producing and marketing of medical devices has to be a specialist in many interdisciplinary realms, ranging from natural sciences to finances and ethics. This requires both curiosity, knowledge and the capability of finding compromises in terms of cost and time. Current main issues represent the following questions: (1) "How to test a device adequately?" (2) How to cope and avoid extractables from polymers and medical devices? (3) How to achieve a reasonable biocompatibility? A good understanding of physiological pathways and processes in the body of a human being helps to answer these questions during conception, research and development of devices for medical application. Last but not least, the bioengineer has to be communicative, because many questions can only be answered in a cooperation between scientists and engineers from both academia and industry.

Introduction

Medical device technology has made an enormous progress in recent years. Diseases can be recognized earlier and therapies initiated faster and more efficiently. It can be explained by both a better understanding of the medical background and knowing the physiological consequences of medical device interaction with parts of the human body. Further, new concepts on improving quality of production and control, cost efficiency and where, when and how to apply medical devices (e.g. invasive or non-invasive) have been advanced and perfectioned. However, a "one-fits-all" medical device does not exist. The patient as a target has to be properly defined and her/his individual needs precisely addressed. It's general knowledge that when looking at possible targets for treatments with medical devices, individual properties of patients in terms of age, gender, possibly genetics and individual malfunctions of the body, have to be recognized. A short overview about functional disorders depending on patient age is provided in Fig. 2.1.

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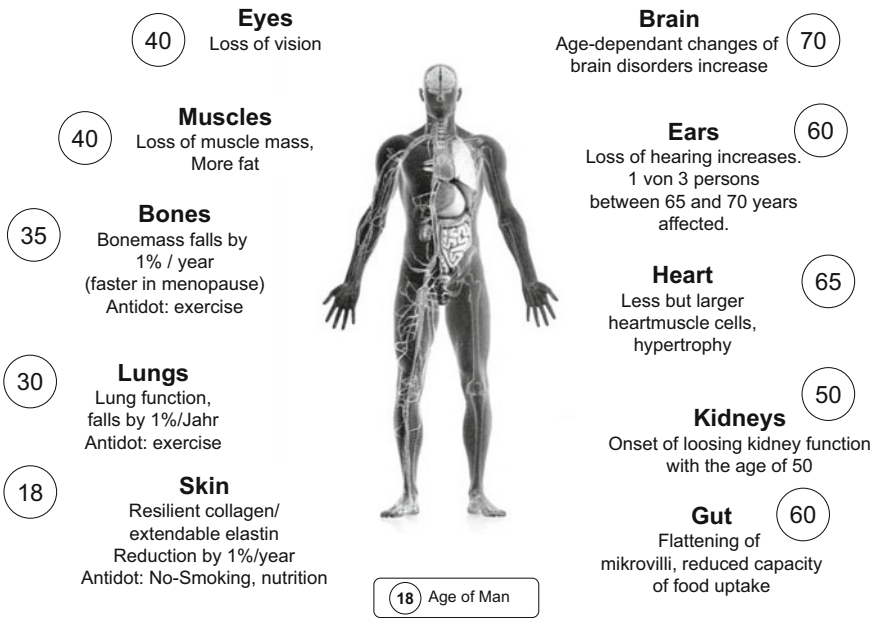

Fig. 2.1 MedTech targets based on the human time-axis. Subsequent failures of body functions are shown. Already at the age of 18 possible therapies to be addressed by medical devices or medicinal drugs may be needed to recover skin failure or for patients at an average age of 50 with first signs of kidney failure. (©: the author)

Bioengineers, who want to apply medical devices for the compensation of malfunctions of body parts, must also bear in mind that the physiology of a patient changes with age. It renders the pre-emptive development of medical devices difficult.

Recently developed innovative techniques with appropriately adapted medical devices have also shown that medical devices are available like body's spare parts. To mention only two of the most spectacular recent developments: an electronic skin which shows both flexibility and a sense of touch, possibly to be applied for the treatment of heavy wounds [1] (and not from the age of 18 onwards (see Fig. 2.1)) and brain-computer interfaces (BCIs) for the communication of people, who have lost the ability to move or speak [2]. Such BCIs help to welcome handicapped people back to a social life by "decoding attempted handwriting movements from neural activity in the motor cortex and translating it to text in real time" [2]. New trends have advanced the use of controlled device performance by an online feedback control through the direct interaction of sensors and monitors. With Artificial Intelligence (AI) techniques, information on sicknesses of global patient cohorts is stored, collected and interpreted as big data. Paralleled epidemiological investigations allow for the prediction of diseases now and in the future, which will possibly allow to predict the needs of medical devices, their properties and performances in times to come.

A promising example stems from the international databank MONDO (Monitoring Dialysis Outcomes across the world [3]). With the retrospective analysis of a huge cohort of patients on haemodialysis, a close relationship between the rise in concentration of an indicator for inflammation (C-reactive protein) and subsequent death could be proven. This allows to ask the question, whether the kinetics of inflammatory signals [4] or the control of fluid status [5] in the time course of a chronic diseases could be influenced by the use of innovative medical devices in order to avoid or delay premature death. Future investigations and innovations will certainly guide us towards this direction.

2.1 Medical Devices, Experiences Skills, Customer Needs and Ethical Impacts

Medical devices and the goal to adapt engineered developments to the individual needs of patients have a long history. It is based on skills and experiences of engineers in collaboration with physicians. In an Egyptian tomb, a wooden big toe prosthesis was discovered which represents possibly the oldest known intravital limb prosthesis [6]. It belonged to a woman, possibly a princess, who died at the age of 55 around 3000 years ago. The prosthesis was artistically shaped and carved with a toenail. Recent investigations have further shown, that the wooden prosthesis had been modified, possibly to be adapted to the specific needs of the female customer. Later in history, physicians experienced the amputation of lower legs and the subsequent leg-support by a prosthesis. For instance, the Christian mythology reports on a leg amputation on a white patient and its replacement by the leg of a black person. The protagonists in charge had been the courageous holy saints Cosmas and Damian [7]. However, to be unconventional and not keeping with the times, their expert behaviour represented a risk of death for such surgeons. Mythology tells us that they have been decapitated later.

Medical therapies have never been for free. A woodcarving from the year 1517, showing the amputation of a lower leg by a barber surgeon, reveals that the operation was controlled by a supervisor standing next, who hold out his hand for a timely compensation [8].

To date bioengineers in charge of developing a medical device may profit from the past and consider those experiences on technology, customer needs, ethical behaviour and cost. These basic conditions have not changed until to date. Despite being sick, the patient remains to be a customer, who is entitled to request excellent performance, reliability and reproducibility of medical devices (MDs) to be provided by the bioengineer. Thus, the knowledge of an engineer in the MD realm has to be very wide as the medical device technology is interdisciplinary. A whole lot of science disciplines are involved here, such as chemistry (polymers), physics (mechanical and electrical, flow pattern of liquids), biology and microbiology (behaviour of cells and tissue), medicine (physiology and treatment modes), hygiene

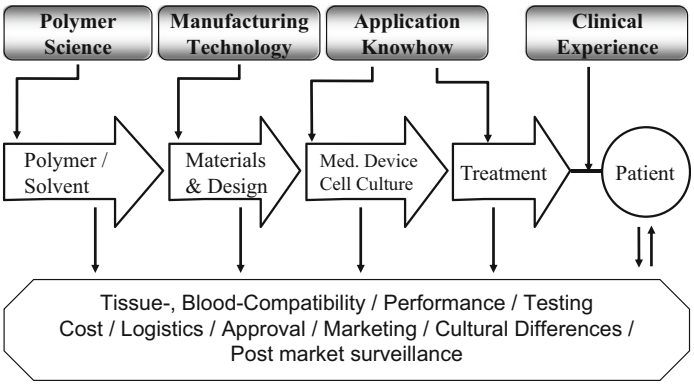

Fig. 2.2 Bioengineers, who develop medical devices, have to be universally engaged in getting knowledge in all disciplines of natural sciences and the determining bystander conditions (lower panel). When being incompetent in one or the other field, a collaboration with suitable specialists is mandatory. A cooperation between academic and industrial institutions has proven beneficial for both parties in many situations and has led to a win-win situation. (©: the author)

(microbial contamination and sterilization), clinical trial experience, certification and approval, managerial skills, as well as an experience in economics, marketing and sales (customer relationship). These requirements look highly universal and a bioengineer in charge of medical device development has to cope with it. Given that this is not achievable for all disciplines, a close collaboration between specialists in different realms will come out successful and include the cooperation between industrial and academic institutions. Therefore, medical device technology is both, interdisciplinary and intercommunicative. Bioengineers, who develop medical devices, are thus also mediators between the above-mentioned disciplines. Figure 2.2 depicts these bioengineering realms (upper panel), developmental chains (centre) and the determining bystander conditions.

2.2 Challenging Issues for Engineers: Reliability of Medical Device Testing

The current market for medical devices is a global business. The involved industry represents not only national interests but has also to face international regulations. No wonder, that customers and patients have to be addressed under varying global aspects. It implies that a “standard customer” or a “standard patient” to whom medical devices are delivered and administrated does not exist. Local conditions, ethnic peculiarities or genealogic facts have to be taken into account, when medical devices are conceived, developed and marketed. New concepts for the application of medical devices are based on the principle of “pay-for-performance”. The capability to measure the corresponding performances thus becomes the number one

requirement. A commonly expressed statement indicates accordingly: "You can only control, what you can measure!" During both research and development of medical devices, as well as during clinical trials for approval, the performance of an instrument and its components (polymers, glues, paintings, codes) have to be assessed under bystander conditions in order to cope with the peculiarities related to age, gender, different ethnics and varying genetical factors. It is interesting to mention in this context that many authors of scientific publications on clinical trials in the USA discriminate between Blacks, Hispanics and Whites. Obviously, such a differentiation is necessary to explain variable results between such cohorts.

2.2.1 The Problem

"Methodology is everything and the devil is in the details!" is a remark of Paul Simmons, the past president of the International Society for Stem Cell Research, in an article in Nature Magazine [9]. P. Simmons refers here to current problems related to the reproducibility of data in stem cell research. Do we have to consider similar thoughts, when speaking about medical devices and their reproducibility? We should not anticipate fraud or manipulation, when data or analyses on the performance of comparable medical devices which are available in the public literature or in scientific publications, differ considerably. In addition, and to the surprise of precisely thinking engineers, evaluations from in vivo comparisons of medical devices or other products in life sciences show standard deviations of up to 100%. This is by far higher than comparable results from common engineering investigations. Obviously, in life sciences impact factors, such as the specific role of an individual patient, the day time of measurement, comorbidities and medication play a determining role. Decisions to be taken by engineers during the time course of developing a medical device have to take these observations into account. Recently and in this context, the allegoric term "Death Valley" was introduced into the field of medical device technology. The term is understood to paraphrase the huge discrepancy between published results from either academic or industrial research.

A medical device must be competitive, functional and reliable. These attributes are usually targeted in preclinical and clinical trials. A low reproducibility and a lack of safety of recently developed medical devices in preclinical investigations corresponds to unfavourable high economic losses, a delayed way to market and a loss of reputation. One of the underlying motives of the new European Medical Device Regulation (MDR) "Better safe than sorry!" reflects the responsibility of engineers to achieve these goals. On the other hand, products originating from academic research and described in scientific publications do not necessarily have to cope with these regulations, as long as they have not been approved. An analysis of scientific articles, which has been published in the journal *PLoS Biology* in 2015, shows that about 50% of published scientific data on medicinal products are not reproducible. As a consequence, economic losses in the referred medical industry added up to 28 billion

US-$. In addition, affected patients were highly disappointed about non-available medical devices [10].

2.2.2 Reasons and Explanations

The above considerations influence decision makers especially in the early phase of medical device development. What can be done to overcome these headache-like situation? A series of factors play a role which have to be identified and compensated by knowledge and both quality and perfection of analytical test systems. For instance, blood/tissue/material- or blood/tissue/ device-interaction play a considerable role during tests of device performance, e.g. when comparing samples from young or elderly persons. In addition, the purity of raw materials, the stability of polymer blends deriving from different sources, packaging materials and the type of device sterilization cannot be neglected. In addition, in vitro testing of materials and devices in the early phase of development is usually performed with blood from healthy donors. The quality of such a liquid for testing depends on the type of donor, his age, gender, possible pre-existing illnesses, circadian influences of blood drawing, and the actual nutrition and medication. For instance, a fatty meal on the evening before donation or the intake of Aspirin affects blood behaviour and test results considerably. As a consequence, standardization of test procedures is a *conditio sine qua non* and knowledge of possible pitfalls, as well as a careful documentation of results, including the hour of experiment completion, is absolutely necessary. The precise selection of tests, as recommended in ISO 10993-4 [11], may help the engineer to be on the safe side for drawing conclusions on performance of materials and devices.

2.2.3 Boundary Conditions for Optimal Testing

Some examples may further illustrate the above statements.

1. The adhesion of platelets to material or device surfaces depends on the respective temperature. This is not surprising. However, differences can be observed, when polymers of varying composition are submitted to experiments and measurements under either room temperature (22 °C) or body temperature (37 °C). Current observations in in vitro experiments have not shown yet any differences [12]; however, in vivo analyses are still pending.
2. It is common practice to test with healthy donor blood, whereas the upcoming clinical application will happen under pathological conditions. As an example, the performance of blood varies considerably when exposed to different shear rates or when in contact with different polymers during perfusion experiments. In detail, blood when donated by diabetic patients, patients with coronary artery

disease or healthy donors shows different levels of fibrinogen or other peptides. This may serve as an explanation for this observation [13].

3. Recent results have shown that platelet derived microparticles (PMPs) emerged as a novel regulator of vascular dysfunction. PMPs are extracellular vesicles released from activated platelets and are found to be widely deposited in podocytes of glomeruli both in diabetic patients and animal models. Their presence is closely associated with the progression of diabetic nephropathy [14]. PMPs are also defined as "micro-vesicles" and contain mRNA and could be thus also applied for medical therapies [15]. Given that PMPs of different patients are generated by the interaction of platelets with devices during perfusion of blood, clinical sequelae—in a positive or negative way—can be expected also during in vivo application. With a pre-emptive analysis of donor blood, consequences of blood/material/device interaction could be understood and interpretations for an engineer made easier.

2.2.4 Conclusion on Testing

The statement "Who cures is right!" should be replaced by "Who measures is right!" during research and development of medical devices. Preclinical in vitro and clinical in vivo test-experiments require a stringent standardization [16]. When using blood as a solution for test-experiments, specific properties of donors, or animals either healthy or sick, should be taken into account [17].

2.3 Challenging Issues for Engineers: Medical Devices and Extractables

"Blood is a very peculiar liquid", stated Mephisto to Faust in the novel "Faust" by the German writer Johann Wolfgang von Goethe. Indeed, blood, which contains electrolytes, enzymes, lipids and proteins apart from water, is capable of extracting leachables from polymers or medical devices in a highly efficient manner. Consequently, biomaterial testing should always examine extraction capacity with the help of appropriate extraction media. One reason for the occurrence of extractables is a shift to a broader molecular weight (MW) distribution during polymer synthesis (Fig. 2.3). Broader MW-distributions give rise to a higher susceptibility of the resulting polymer for extractables.

Polymer ageing adds to the source of extractables as well as the degradation of some polymers in a wet atmosphere or after some sterilization procedures. Medical devices undergo degradation processes given that they are implanted for a long-term period in the human body. This also holds true for those chronic patients who are treated by extracorporeal blood purification systems, such as haemodialysis. Here, medical devices are chronically exposed to blood, serum or interstitial liquids that

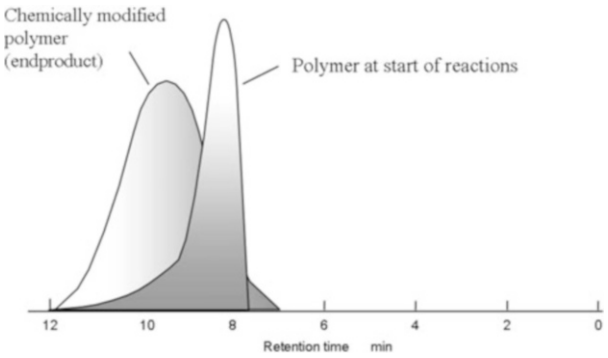

Fig. 2.3 Molecular weight distribution of a polymer before and after the chemical reaction assessed by gel permeation chromatography (GPC) analysis. A wider molecular weight distribution (left) gives rise to a higher level of extractable oligomers. (©: the author)

provoke polymers to be degraded, saponified in the case of ester compounds or promote the release of spallation particles as observed in the case of silicon tubing. During the development of new medical devices, engineers should thus focus on possible degradation products that may be released from polymeric material into body tissue, blood or organs to avoid long-term complications.

2.3.1 How are Extractables Defined?

Extractables are chemicals that are generated under exaggerated temperature and time conditions in the presence of an appropriate solvent. **Leachables** are chemicals that migrate spontaneously from a container-closure system (e.g. blister), from packaging components and/or from processing equipment under recommended or routine conditions of use and storage. Leachables are often a subset of extractables.

Adverse clinical reactions initiated by extractables are not exclusively found after the exposure of polymers to human blood or tissue. Even metallic devices, which are generally considered to behave neutrally, are able to provoke adverse clinical reactions as shown by the following example.

2.3.2 Case Report on an Artificial Hip

A year and longer lasted the problems of a patient, when his physicians discovered a cobalt intoxication originating from a previously implanted artificial hip. The patient suffered from severe heart failure and both fever with unknown origin and enlarged lymph nodes. A careful anamnesis revealed that the patient's ceramic-on-ceramic hip prosthesis had been replaced by a metal-on-polyethylene prosthesis around

15 months before. Laboratory analyses showed a nearly 1000-fold increase in the concentration of cobalt and chromium ions in his blood, combined with some metal debris at the left-sided hip. Obviously, remaining ceramic particles from his first prosthesis have destroyed the metal head of the hip replacement [18] and had led to these deleterious findings.

Chronically sick haemodialysis patients are another cohort, that may suffer from leachables released into their organism. Dialysis patients are repeatedly exposed to an extracorporeal blood circuit that is made up from tubing, syringes and filters for many years. By this means, extractable materials may accumulate in the body of these patients and induce adverse clinical effects. In recent years, this treatment has reached perfection by using pure raw materials, avoiding the release of components from medical devices, e.g. a special type of plasticizer. However, it can be expected that effects based on extractables will increase in number, given the rise in the number of dialysis patients in recent years. For instance, in Japan more than 25,000 patients are currently undergoing this therapy already for more than 20 years [19]. Thus, leachables originating from the dialysis system, in particular from polymers in the extracorporeal blood circuit are now a matter of interest.

2.3.3 Observations from Experiences on Haemodialysis Treatments

The extracorporeal blood circuit used for dialysis therapy is engineered from polymers representative for most medical devices, such as polycarbonate, silicone, polypropylene (PP), polysulphone (PSu) and polyurethane (PUR). During medical application, these polymers are exposed to body liquids, such as plasma or whole blood. Apart from blood cells, both, human and animal blood contains water, electrolytes, proteins, hormones, and enzymes (Table 2.1). Due to these compounds, both, "blood plasma" or "whole blood" are able to wet any biomaterial independent of its chemical composition, whether hydrophilic, hydrophobic or with an amphiphilic domain-like surface. Blood in contact with biomaterials offers an ideal chemical environment for extracting substances from bulk polymers, e.g. oligomers or biodegradable compounds. Body liquids possess ideal solvent-like properties. As a consequence, leachables may accumulate in the body, in particular in the body of long-term chronically exposed patients.

In its revised edition from 2009, ISO 10993-1 recommends to consider extractables and degradation products during the biological evaluation process of medical devices [20]. Problems arise, however, how to simulate the extractive capacity of blood? ISO 10993-12 (Art 4) provides the answer: "the solvent selected as extractants shall: (a) be suitable for use in the specific biological test system; (b) simulate the extraction which occurs during clinical use of the device and/or (c) maximize the amount of the extract".

Table 2.1 Blood is composed of plasma and cells

Plasma (> 1300 compounds)	**Blood cells**
1. **Proteins (8%)** Among others: – Albumin (50%) – Immunoglobulins (antibodies, 35%) – Fibrinogen (5%) 2. **Water** 3. **Inorganic salts**; electrolytes 4. **Further compounds** Hormones, fat, carbohydrates, enzymes	1. **Erythrocytes** (red blood cells, 4–5 × 10^{12}/L) 2. **Thrombocytes** (platelets, 150–380 × 10^{9}/L) 3. **Leukocytes** (white blood cells, 6–8 × 10^{9}/L) (T-cells, B-cells, granulocytes, polymorphonuclear cells, eosinophils, macrophages, monocytes, killer-cells)

Plasma contains water and fat, electrolytes, carbohydrates, proteins and enzymes. This composition allows for wetting surfaces of all biomaterials and devices, independent of their chemical composition, either hydrophilic or hydrophobic. Blood and other body liquids are perfect media to provoke the extraction of any loosely bound material or polymeric contaminants

The following media for extraction are suggested and one per type should be subsequently and not exclusively used in an extraction experiment:

1. Polar solutions (water, saline (0.9% NaCl in water), culture media without serum).
2. Unpolar solutions (vegetable oil, e.g. Sesame oil).
3. Additionally: polyethylene glycol (PEG 400), dimethyl sulphoxide (DMSO), culture media with serum, alcohol/water mixtures.

Experiences in my laboratory have shown that mixtures of 20/100% EtOH/H_2O provide optimal results when a transparent solution is needed to simulate the behaviour of blood.

Further, a practical guide and scheme for testing medical devices is provided in ISO 10993-17 [21]. Allowable limits for leachable substances in biomaterials are addressed in ISO 10993-12 [22].

2.3.4 Examples for Adverse Clinical Effects in Patients

Already in the 1980s, leachable ethylene-oxide (ETO) after gas-sterilization of medical devices, provoked severe allergic reactions in hypersensitive patients. Physicians defined these reactions as a “first-use syndrome”, because they disappeared either after a careful rinsing or after re-use of the device. ISO 10993-7 refers to maximum allowable ETO-residuals [23]. Further, some compounds, such as the plasticizer Bis(2-ethylhexyl)-phthalate (DEHP) or residuals from polycarbonate (PC), polysulphone (PSu) or some resins, such as Bisphenol A (BPA) or Bisphenol S (BPS) may interact with hormone receptors at the surface of biological

cells. By this means hormone-like signals are induced after the leaching of BPA and BPS from medical device polymers. Although DEHP and the bisphenols are not hormones, they are called "exogenous hormones" or "endocrine disruptors" due to their hormone-like capacity to bind also to hormone receptors. According to the EU, DEHP meets the criteria for classification as toxic for reproduction (category 1B) in accordance with regulation (EC) Nr. 1272/2008 and should thus not be present in medical devices applied to adolescents and breast-feeding women, among others [24].

Leachables may also be found to occur during the ageing process of polymers. This is a further argument in favour of an **expiry date** for medical devices. Scientists from the US Centers for Disease Control, Prevention and Radiological Health (CDC) reported in 2000 [25] that a severe and unusual outbreak of serious neurological signs and symptoms occurred in 5 out of 7 patients in association with the use of 10-year-old dialysers with passed expiry dates. All patients exposed to these filters developed an acute onset of diminished vision and hearing. Four case patients never recovered. The authors explained these findings with material degradation of the cellulose-acetate polymer, as the average molecular weight decreased from 40,000 to 30,000 in the dialysers tested and referred to either de-acetylation (saponification) or chain scission of the polymer [25].

To the surprise of many medical device manufacturers, even quality management measures, if not carefully prepared, may result in fatal incidences. As reported in a series of publications in 2001 and 2002, 23 dialysis patients died in Croatia as a consequence of the repair of a medical device (dialysis filter) in the production process realized with a performance test for leaky capillary membranes: the test was performed with the help of a perfluorocarbon-5070 liquid [26]. Residual amounts of PF5070 stayed in the filter and were rinsed out by the perfusing blood during the subsequent dialysis therapy. PF5070 slowly accumulated in heart and lungs of the patients where it caused their death several hours later by foam formation.

2.3.5 Conclusion on Extractables

Leachables and extractables from polymers, biomaterials and medical devices should be carefully assessed, once they are exposed to body liquids in long-term clinical application. Associated adverse events may lead to severe allergic reactions or even fatal consequences. The amount of residual extractables in medical devices should, thus, be kept as low as possible. Open questions, however, still remain to be answered, e.g. what are the threshold levels for leachables below which no adverse events can be detected? Or: "How to control the release of leachables in long-term chronic patients?" As long as these questions remain open, careful clinical observations and a detailed understanding of the underlying mechanisms is mandatory.

2.4 Challenging Issues for Engineers: Medical Devices and Biocompatibility

Bioengineers in charge of medical development have to be familiar with device properties in terms of biocompatibility pattern, because devices in contact with body structures may provoke physiological reactions. Surface reactivity and intrinsic properties of biomaterials and devices determine device- or material-biocompatibility. However, the term "biocompatibility" has turned out to become a buzzword and is used in many cases without any detailed background information on the type of device, its composition and clinical application. It is reasonable to cite here the definition of the European Society for Biomaterials from 1993 to have a closer insight:

> "Biocompatibility is the ability of a material to perform with an appropriate host response in a specific application".

Consequently, biocompatibility pattern of a device cannot be generalized. These characteristics depend on the type of device, its specific application and even on the very disease or situation of a patient. When therefore reporting on the biocompatibility of a medical device, careful distinctions have to be made whilst avoiding a "generally speaking". In addition, controversies have come up how to define interactions between body liquids and materials/devices. ISO 10993-4 from 2009 [27] reflects about classification of interactions, such as:

> Interactions which mainly affect the device and *which may or may not have* an undesirable effect on the subject as follows:
>
> 1. Adsorption of plasma proteins, lipids, calcium or other substances from the blood onto the surface of the device, or absorption of such substances into the device.
> 2. Adhesion of platelets, leukocytes, or erythrocytes onto the surface of the device, or adsorption of their components into the device.
> 3. Formation of a pseudointima or tissue capsule on the surface of the device.
> 4. Alterations in mechanical and other properties of the device.

It is still a matter of debate, whether interactions *may or may not have* an undesirable effect. The authors understanding is that biocompatibility assessments should be done as close as possible to the intended clinical application, and therefore, biocompatibility pattern should describe preferentially "undesirable effects".

Investigative research has identified many factors for the assessment of biocompatibility. However, no clear-cut conclusion has been derived which of these factors would yield the most reproducible results. A short overview, provided in Fig. 2.4, shows that we have to discriminate three main areas, such as inflammation, allergy and immune system and coagulation.

In addition, Table 2.2 provides examples of medical devices and their specific characterization in terms of biocompatibility testing.

It is the intention of many investigators to obtain an overall score when assessing biomaterials or medical devices. A score could be a compromise for a fast characterization and help decision-making. Such a score has been recently developed [28].

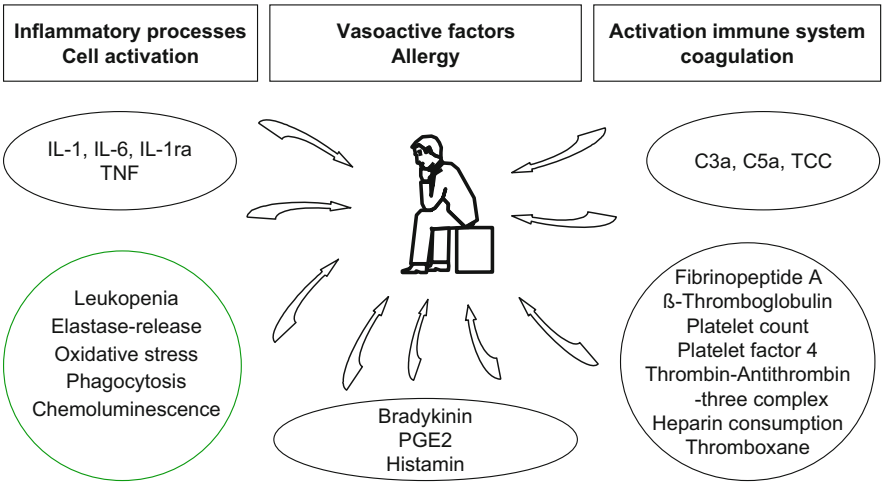

Fig. 2.4 Three main areas should be applied for the characterization and assessment of biocompatibility pattern of a material or a device: Inflammatory processes (Interleukin l, IL-1, Interleukin 6, IL-6, and Tumour Necrosis Factor, TNF), vasoactive factors (Prostaglandin E_2, PGE_2) and allergy, as well as the activation of both the immune system and the coagulation cascade. Factors representing the plasmatic immune system, i.e. the Complement System: C3a, C5a, TCC. (©: the author)

Table 2.2 Proposed features for biocompatibility testing of specific medical devices

Device examples	Thrombosis	Coagulation	Platelets	Haematology	Complement system
Atherectomy devices				x[a]	
Blood monitors	x			x[a]	
Blood storage and blood collection devices, extension sets		x	X	x[a]	
ECMO and HD systems	x	x	X	x	x
Percutaneous systems					
Catheters, guidewires, endoscopes, intravascular ultrasound, laser systems	x	x		x[a]	
Cell savers		x	x	x[a]	
Devices for adsorption of specific substances from blood		x	x	x[a]	
Donor and therapeutic Apheresis equipment		x	x	x	x

Adapted from [27]
[a]Haemolysis testing only

In the following those biocompatibility aspects of biomaterials which provoke clinical consequences are described in short.

2.4.1 Thrombogenicity and Blood Coagulation

Artificial surfaces are able to stimulate platelet activation and the coagulation cascade. Modern polymers/biomaterials exhibit a considerably reduced thrombogenic potential. Apart from chemical polymeric properties, the geometric design of flow paths, e.g. in capillary membranes or small flexible tubes and a possible contact of blood with air bubbles may affect coagulation pathways and lead to the formation of blood clots. Haemoconcentration, as observed after filtration processes, like in haemodialysis or in plasmapheresis, may further lead to the formation of blood clots. The best advanced parameter for assessing coagulation is the analysis of the Thrombin-Antithrombin III Complex (TAT).

2.4.2 Stimulation of the Immune System (Complement- and Cell-Activation)

Complement activation represents the classical parameters of biomaterial bioincompatibility. Its alternative pathway depends on the presence of nucleophilic surface moieties. Complement activation by biomaterials or surfaces depends on their surface chemistry. For instance, the presence of hydroxyl-groups (OH-groups) on a materials surface leads to an ester binding of the complement protein C3b, which initiates the autocatalytic alternate pathway of the complement cascade. A chemical modification of biomaterial surfaces through the substitution, of such hydroxyl-groups, by ester or ether groups prevents complement activation. Adverse events are mainly seen, when complement activation is twinned with the presence of endotoxins from bacterial cell walls. Here, cytokines are released in a synergistic manner from white blood cells (cell-activation), which may lead to inflammatory reactions.

2.4.3 Hypersensitivity Reactions

Allergic reactions are frequently observed in those patients, who have been in contact with residuals of the sterilizing agent ethylene-oxide (ETO). ETO is bound spontaneously to the blood protein albumin. Due to its then higher molecular weight, ETO provokes the formation of IgE-antibodies, which are responsible for the majority of seen hypersensitivity reactions. Biomaterials such as polyurethane

(PUR) and poly-methyl-methacrylate (PMMA) store ETO in their bulk structure and show a slow-release pattern. Apart from ETO, polymer extractables (e.g. oligomers) or other compounds from medical devices used in extracorporeal blood purification systems [29] are eluted with the help of blood and may induce hypersensitivity- or adverse reactions, as observed with cellulose extracts (1.4-ß-glucans), perfluorocarbons, isocyanates from PURs, or plasticizers. It is still a matter of controversy, whether these compounds are able to induce acute effects in humans or not. Clinical consequences in chronically treated patients, such as those treated with haemodialysis, however, have to be seriously considered.

2.4.4 Haemodynamic and Vasoactive Effects

Surfaces bearing negative charges of a defined charge-density stimulate the "contact phase" of coagulation. As a consequence, the vasodilator bradykinin is formed and—if not degraded by ACE (angiotensin-converting enzyme)—severe blood pressure drops are observed. This happens mainly in those patients, who are treated by ACE-inhibitors. Some polymers made from either polyacrylonitrile-blends or dextran-sulphate show these effects and have exerted fatal incidences in many patients treated by haemodialysis or apheresis [30, 31]. Similar observations can be made during reprocessing of medical devices, when oxidation of adsorbed proteins give rise to the formation of negative charges of a defined density at material surfaces.

2.4.5 Conclusion on Biocompatibility

Biocompatibility pattern have to be analysed systematically. They refer to all components of a device, such as polymers and their blends, the geometry and stability of a device itself under storage or during clinical application and last but not least to treatment modality and the specific situation of a patient (Fig. 2.5). It is possible to adapt the polymer composition of modern biomaterials in such a way that adverse patient reactions can be excluded or at least be minimized. This is the consequence of a better understanding of the underlying mechanisms of blood material interaction. In addition, both, smart geometries and design of biomaterials and avoiding sterilization with ethylene oxide gas through steam sterilization are the strategies for further biomaterial development [32, 33].

Biocompatibility pattern has to be analysed systematically. They refer to all components of a device, such as polymers and their blends, the geometry and stability of a device itself under storage or during clinical application and last but not least to treatment modality and the specific situation of a patient. This is an ideal example for the application of a system approach in medical device development.

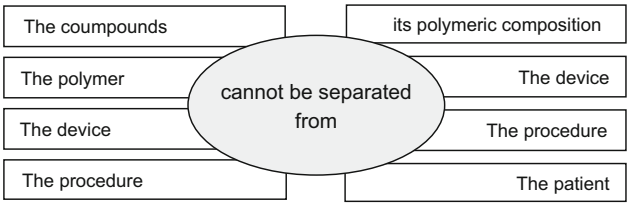

Fig. 2.5 Biocompatibility pattern has to be analysed systematically. They refer to all components of a device, such as polymers and their blends, the geometry and stability of a device itself under storage or during clinical application and last but not least to treatment modality and the specific situation of a patient. (©: the author)

Conclusion

The engineer in charge with developing, producing and marketing of medical devices has to be a specialist in many interdisciplinary realms, ranging from natural sciences and engineering to finances and ethics. This requires both curiosity, knowledge and the capability of finding compromises in terms of cost and time. Current main issues represent the following questions: (1) "How to test a device adequately?" (2) How to cope and avoid extractables from polymers and medical devices? (3) How to achieve a reasonable biocompatibility? A good understanding of physiological processes in the body of the human being helps to answer these questions during conception, research and development of devices for medical application. Last but not least, the bioengineer has to be communicative, because many questions can only be answered in a cooperation between scientists and engineers from both academia and industry.

Take Home Message

- The interdisciplinarity and continuously innovative field of medical device technology requires extended knowledge of the engineers in charge of developing such devices.
- Development of devices needs to apply adequate and standardized testing procedure not neglecting the special physiological properties of a sick patient.
- Extractables from materials and devices play an important role in safety and stability considerations of medical devices.
- Biocompatibility of materials and devices directly affects the patient's well-being.
- A close cooperation and communication between academia and industry helps to answer unsolved questions.

References

1. Sanderson K (2021) Electronic skin: From flexibility to a sense of touch. Nature 591:685–687
2. Willet F, Avansino D, Hochberg L, Henderson J, Shenoy K (2021) High performance brain-to-text communication via handwriting. Nature 593:249–254
3. von Gersdorff G, Usvyat L, Marcelli D, Grassmann A, Marelli C, Etter M et al (2013) Monitoring dialysis outcomes across the world – The MONDO global database consortium. Blood Purif 36:165–172
4. Usvyat L, Barth C, Bayh I, Etter M, von Gersdorff G, Grassmann A et al (2013) Interdialytic weight gain, systolic blood pressure, serum albumin, and C-reactive protein levels change in chronic dialysis patients prior to death. Kidney Int 84:149–157
5. Dekker M, Marcelli D, Canaud B, Carioni P, Wang Y, Grassmann A et al (2017) Impact of fluid status and inflammation and their interaction on survival: A study in an international hemodialysis patient cohort. Kidney Int 91:1214–1223
6. Samples R (2001) Mummy has a wooden toe. Science 291:243
7. Becker C (1914) Die Wunderheilung der Ärzteheiligen Cosmas und Damian. Dtsch med Wschr 40:27–28
8. Hans von Wechtlich (1517) Feldtbuch der Wundartzney. Strassburg 1517
9. Check E (2007) The hard copy. Nature 446:485–486
10. Freedman et al (2015) The economics of reproducibility in preclinical research. PLoS Biol 13(6):e1002165
11. International Standard Organisation (2009) (DIN EN ISO) 10993–4. Biological evaluation of medical devices – Part 4: Selection of tests for interactions with blood
12. Braune S, Fröhlich G, Lendlein A, Jung F (2015) Effect of temperature on platelet adherence. Clin Hemorheol Microcircul 61:681–688
13. Braune S, Groß M, Walter M, Zhou Z, Dietze S, Rutschow S, Lendlein A, Tschöpe C, Jung F (2016) Adhesion and activation of platelets from subjects with coronary artery disease and apparently healthy individuals on biomaterials. J Biomed Mater Res Part B 104:210–217
14. Zhang Y, Ma K, Gong Y, Wang G, Hu Z, Liu L, Lu J, Chen PP, Lu CC, Ruan X, Liu BC (2018) Platelet microparticles mediate glomerular endothelial injury in early diabetic nephropathy. J Am Soc Nephrol 29:2671–2695
15. Cantaluppi V, Gatti S, Medica D, Figliolini F, Bruno S, Deregibus M, Sordi A, Biancone L, Tetta C, Camussi G (2012) Microvesicles derived from endothelial progenitor cells protect the kidney from ischemia–reperfusion injury by microRNA-dependent reprogramming of resident renal cells. Kidney Int 82:412–437
16. Vienken J (2010) Biomaterials for medical devices: are current hemo- or biocompatibility tests adequate? Mat Wiss u Werkstofftech 41:1081–1085
17. Mueller X, Tevaearai H, Jegger D, Tucker O, von Segesser L (2001) Hemolysis and hematology profile during perfusion: Inter-species comparison. Int J Artif Organs 24:89–94
18. Dahms K, Sharkova Y, Heitland P, Pankuweit S, Schaefer R (2014) Cobalt intoxication diagnosed with the help of Dr. House. Lancet 383:574–575
19. Nitta K, Goto S, Masakane I, Hanafusa N, Taniguchi M, Hasegawa T, Nakai S, Wada A, Hamano T, Hoshino J, Joki N, Abe M, Yamamoto K, Nakamoto H (2020) Annual dialysis data report for 2018, JSDT Renal Data Registry: survey methods, facility data, incidence, prevalence, and mortality. Ren Replacem Ther 6:41
20. ISO 10993-1 (2009) Biological evaluation of medical devices: Part 1. Evaluation and testing within a risk management process
21. ISO 10993-12 (2003) Biological evaluation of medical devices: Part 12. Sample preparation and reference materials
22. ISO 10993-17 (2002) Biological evaluation of medical devices: Part 17. Establishment of allowable limits for leachable substances. (New ISO under development 2021)
23. ISO 10993-7 (2009) Biological evaluation of medical devices: Part 7. Ethylene-oxide sterilization residuals. Edition 2009

24. Commission regulation (EU) Nr. 143/2011 of 17 February 2011. Off J European Union, L44/2 from February 18, 2011
25. Hutter J, Kuehnert M, Wallis R, Lucas A, Sen S, Jarvis W (2000) Acute onset of decreased vision and hearing traced to hemodialysis treatment with aged dialysers. JAMA 83:2128–2134
26. Canaud B, Aljama P, Tielemans C, Gasporovic V, Gutierrez A, Locatelli F (2002) Performance liquid test as a cause for sudden deaths of dialysis patients: perfluoro-hydrocarbon, a previously unrecognized hazard for dialysis patients. Nephrol Dial Transplant 17:545–548
27. ISO-Standard 10993–4 (1993) Biological evaluation of medical devices
28. Erlenkötter A, Endres P, Nederlof B, Hornig C, Vienken J (2008) Score model for the evaluation of dialysis membrane hemocompatibility. Artif Organs 32:962–968
29. Gwinner W, Menne J, Lonnemann G, Bahlmann F, Koch K, Haller H (2005) Life-threatening complications of extracorporeal treatment in patients with severe eosinophilia. Int J Artif Organs 28:1224–1227
30. Tielemanns C, Madhoun P, Lenaers M, Schandene L, Goldman M, Vanherweghem JL (1990) Anaphylactoid reactions during hemodialysis on AN69 membranes in patients receiving ACE inhibitors. Kidney Int 38:982–984
31. Kammerl M, Schaefer R, Schweda F, Schreiber m, Riegger G, Krämer B (2000) Extracorporeal therapy with AN69 membranes in combination with ACE-inhibition causing severe anaphylactoid reactions: still a current problem? Clin Nephrol 53:486–488
32. Vienken J (2001) Polymers in dialysis: characteristics and needs. Med Device Technol 12:18–27
33. Vienken J, Bowry S (2002) Quo vadis dialysis membrane? Artif Organs 26:152–159

Chapter 3
Essentials of Innovation Theory for Medical Devices

Ulrike Löschner and Steffen Fleßa

Abstract Even brilliant medical devices will not become successful on the market unless its associated innovations have overcome a number of barriers. In particular in healthcare, new medical devices have to be approved by recognized authorities and financed by interested stakeholders. Thus, planning, implementing and controlling the innovation process, from the early idea to the market introduction, is a prerequisite of a successful product life cycle. The knowledge of the different types of innovation processes and the respective barriers for a successful implementation supports decision-makers to overcome these barriers.

Introduction

Even brilliant medical devices will not become successful on the market unless its associated innovations have overcome a number of barriers. In particular in healthcare, new medical devices have to be approved by recognized authorities and financed by interested stakeholders. Thus, planning, implementing and controlling the innovation process, from the early idea to the market introduction, is a prerequisite of a successful product life cycle. The knowledge of the different types of innovation processes and the respective barriers for a successful implementation supports decision-makers to overcome these barriers.

3.1 Healthcare Innovation

3.1.1 Presentation of the Problem

Healthcare systems are characterized by a constant change. For one, this relates to the legal framework that shapes the market as well as the variety of the healthcare

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providers and the services they offer. The challenges for a society can be faced by innovative healthcare products, treatment options and care concepts [1].

Innovation is a very broad term which is not defined explicitly in literature [1]. The widely accepted definition by Schumpeter describes innovation as any change in methods of production, manufacturing of new products, corporate structure or entering a new market. Building on this, the definition by Vahs and Brem applies more specifically to novelties in the healthcare sector. It states that innovation is the initial commercial implementation of a new idea as well as the economic optimization of knowledge utilization [2]. According to that, a narrower definition of innovation concerns the successful introduction into the market. In a broader sense, innovation describes the remaining of an invention in the designated market in the long term. In this context, it is necessary to distinguish between the terms *invention* and *innovation*. The former merely includes the generation of an idea as well as the first technical realization thereof (e.g. a prototype) [3]. The latter term refers to the more comprehensive process starting with generating ideas and ending with the successful acceptance by potential users (adoption) [4]. Inventions are called innovations as soon as they are adopted by the majority of all concerned elements within a system [5].

The healthcare system is shaped by several specific characteristics. For one, the entry into this sector is strictly regulated. Every medical device introduced to the European market currently requires a so-called Conformité Européenne (CE) marking. By this, the manufacturer proves that his product meets the legal standards concerning safety, performance and benefits as well as monitoring of the entire product life cycle [6]. Financing innovative products and services in the healthcare sector is directly linked to this. In case of the German healthcare market, it becomes apparent that only those innovations can persist in the market that can be reimbursed by the statutory health insurance (SHI). New drugs, for example, must prove an additional benefit to the patient compared to existing options of therapy in order to be reimbursed by the statutory health funds (Art. 1 Abs. 5 Arzneimittelmarktneuordnungsgesetz, i.e. Law for the market rearrangement of medicinal products). Only in this way, pharmaceuticals can reach a broad application in the long term. Alternatively, they are suitable only for the markets of privately insured and the self-payers, which are considerably smaller and heavily influenced by decisions of the SHI [7].

In addition, the healthcare economy is characterized by numerous groups of stakeholders. This sector does not show a simple seller–buyer relationship, as is often the case in the private sector. In most cases, the patient is not the direct client, but much rather physicians, therapists as well as the management of hospitals have a considerable influence on the implementation of certain treatment concepts. Other important stakeholders in the health economy are researchers and developers, companies of the industries of pharmaceuticals and medical technologies, the before mentioned statutory and private health insurances, state and federal governments as well as relatives of patients and the society as a whole [8]. The coordination of partly diverting interests of those groups and the use of appropriate communication methods is a crucial factor in this sector. It must also be mentioned that the healthcare sector in many countries comprises many small, mainly regionally operating organizations, research facilities and hospitals [7, 9].

In general, different types of innovation can be distinguished. A differentiation between micro-, meso- and macro-innovations can be made [10]. Innovations on a micro level are merely changes of a few system elements [11]. In healthcare, this essentially means novelties that directly affect the diagnosis and treatment of patients. As soon as additional stakeholders than the ones involved in the physician–patient relation are concerned and adaptions to the structural organization of the healthcare system are necessary, it is considered a meso-innovation [10, 11]. Macro-innovations have extensive consequences on the legal framework as well as values of society as a whole [10]. Regarding this distinction, it becomes eminent that the chance of adoption of a micro-innovation, compared to innovations in the macro level, is significantly higher [11].

Based on this, novelties can be differentiated according to the type of service offered. Table 3.1 shows those categories that are of special importance with regard to the healthcare sector.

Table 3.1 Categorization of healthcare innovations

Product innovations	*Description:* This type of innovation is characterized by an increase in benefit compared to existing goods and competing products [12]
	Goal: The main goal of this type of innovation is the augmented effectiveness the user achieves [1]. Additionally, an advantage in cost-benefit ratio over competitive products can be achieved [13]
	Healthcare Sector: Examples in the healthcare sector are novel drugs, medical devices and combination products
Service innovations	*Description:* This category can be understood as a subgroup of product innovations based on a service as an immaterial good [13]. Service innovations are defined as novel, intangible, heterogeneous and non-storable goods [1]
	Goal: Comparable to the goals of product innovations, mainly improvement in benefits for customers and achieving leadership position in the relevant market [13]
	Healthcare Sector: Service innovations of special significance in the healthcare sector due to the fact that producing and providing a service, for the most part, takes place at the same time and in the same place, requiring the presence of the recipient of a service [14]. Typical healthcare related examples are alternative methods of diagnosis and treatment
Process innovations	*Description:* These innovations are defined as significant changes in the process of production as well as in service provision [2]
	Goal: Increasing efficiency as well as promoting productivity and cost-effectiveness is in the focus of process innovations [13]
	Healthcare Sector: This comprises for example the introduction of quality management systems or standard operating procedures (SOPs)
System innovations	*Description:* Novelties of an organizational nature characterize system innovations, meaning remarkable changes of the current system that have effects on a large number of its elements [1]
	Goal: More efficient allocation of scarce resources and thereby creating a sustainable system
	Healthcare Sector: In a healthcare setting, this refers to alterations not only with regard to the organization of a healthcare system as a whole, but also within a region or a single hospital

The underlying problem of innovations in a healthcare setting is their adoption, meaning their translation into the system as part of a standard approach to treating an illness. Improved clinical results, as well as a higher patient benefit, combined with an increase in cost efficiency compared to the current standard of treatment, are crucial criteria for the acceptance of a healthcare innovation [15]. Improved clinical results are measured by a reduction in mortality, reduced rates of rehospitalization and a shorter length of stay in hospitals [7]. From the perspective of the patient, the most feasible and therefore most relevant results of a treatment are improvements of their specific and overall state of health combined with an increase in the health-related quality of life (QoL).

The adoption of an innovation is a highly complex and multi-stepped process which is mainly shaped by a fair amount of uncertainty regarding the long-term success of the novelty in the market. Various factors can hinder, slow down or even prevent the adoption of the innovation altogether. These obstacles are referred to as innovation barriers [16]. As a result, new concepts of treatment are often broadly implemented in patient care only years after their actual development (Fig. 3.1).

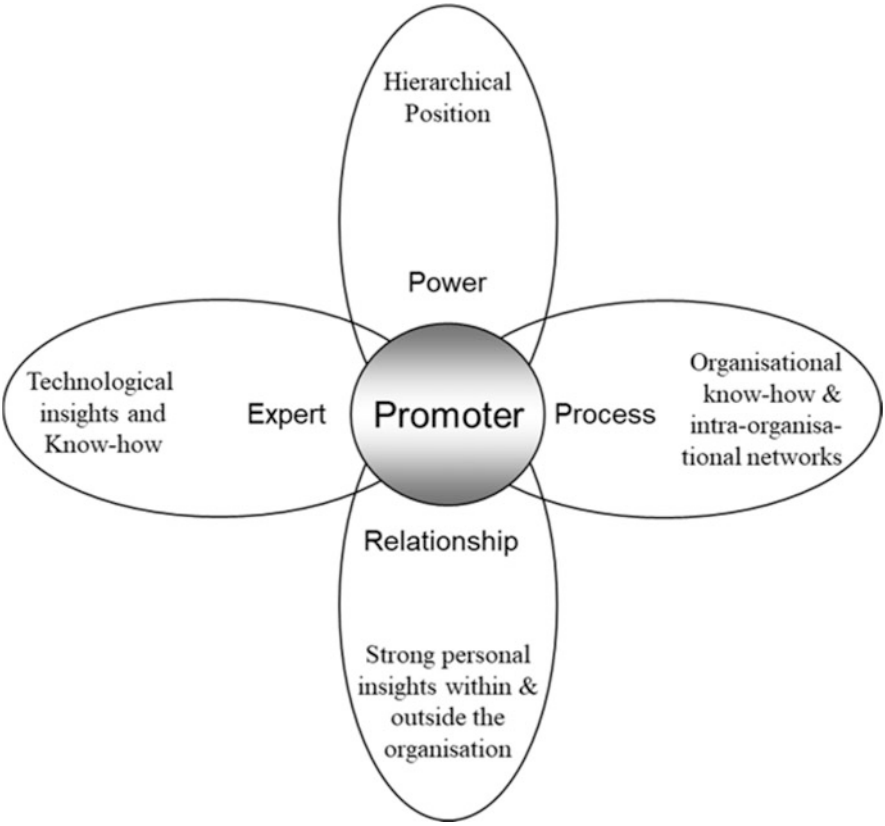

Fig. 3.1 Innovation promoter network based on [17]

Additionally, promoters considerably shape the innovation process. Key people, who influence the adoption of a novelty in a positive manner and thus promote innovation, are referred to as promoter [18]. Different types of promoters have different roles. E. Witte came up with a promoter model that differentiates between *expert promoters* and *power promoters* [18]. The expertise of the former contributes significantly to overcoming the barrier of lacking know-how [19]. This cannot only affect the development of an innovation but also its introduction into specific markets [17]. Contrary to that, the power promoter helps to overcome the barrier of unwillingness. This type of promoter makes essential decisions regarding allocation of available time, financial and human resources and can shape the innovation process accordingly [1]. Based on this model, further promoters can be identified. Hauschildt and Chakrabarti added the *process promoter* whose task is to overcome administrative barriers [20]. Market entry regulations, for example, are very consequential in the healthcare sector and are thus of principal importance. Additionally to know-how on administrative regulations, process promoters are often part of intra-organizational networks and thereby able to connect *expert promoters* to *power promoters* as well as other individuals of importance in the innovation process [21]. Furthermore, in recent decades the significance of adequate ways of communication within an organization but also to stakeholders outside the organization has become more apparent [22]. Especially considering the numerous stakeholders involved in the healthcare sector, a *relationship promoter* is of high importance in order to overcome barriers of lacking or misguided communication between the organization, customers and other stakeholders [23].

In conclusion, the development and implementation of an innovation is a complex process in which *promoters* have to overcome several barriers. Therefore, a structured management approach is a key necessity.

3.1.2 Innovation Management as an Approach to Solution

Successful businesses do not leave the development, introduction to the market and implementation up to chance but they rather systematically plan, organize and control the entire process [24]. The necessity for this arises from the scarcity of resources over all phases of innovation. The objective is to allocate the available financial, material, personnel and time resources in the most efficient possible way in order to ensure the remaining in the market in the long run [2]. Innovation management is therefore in alignment with the requirements of a novelty and includes tools of planning, decision-making, organizing and controlling this process. In this context, Vahs and Brem define different core tasks of innovation management [2]:

- Specification of objectives and strategies.
- Compliance with these objectives and defined strategies.
- Identification of innovation potentials.
- Consideration of the principle of economic efficiency.

- Definition of a sustainable research and development programme.
- Development of a controlling system.
- Creation of an innovation-promoting corporate culture and organizational structure.
- Integration of an IT system over the entire process.

The complexity of innovation management is illustrated by the range of its tasks. Every single task has a central role in successfully implementing an innovative good or service. This is of great significance, especially in the healthcare sector, which is characterized as a network of numerous stakeholders coming from various institutions on different levels of the overall system. In addition, the success of an innovation substantially depends upon early planning and well-structured communication between individual stakeholders [9].

3.2 Model of Innovation Adoption

3.2.1 Overview

To support planning activities in the context of innovation management, the visualization of the entire process can be made based on theoretical models. As a basis for adopting innovations in the healthcare sector, the model according to Fleßa can be applied. Figure 3.2 portrays this general model of health innovation adoption. It supports the identification of barriers and their influence on the adoption process as well as the appropriate placement of available instruments in order to overcome those [25].

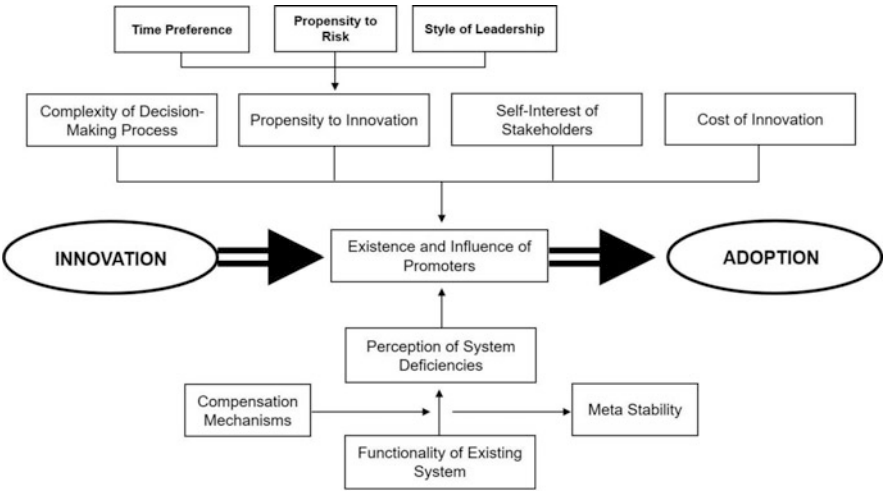

Fig. 3.2 General model of adoption of healthcare innovations, based on [25]

The existence of key persons, so-called promoters as shown in Fig. 3.1, has a substantial role in the success of a novelty. It should be measured in what way they influence the development of an innovation, the process of decision-making, the introduction into the market and all other in between steps and it should also be estimated how that influence can be channelled in a positive way [1].

The model displays four additional, highly relevant, influencing factors for the acceptance of an innovative idea. The first one mentioned is the complexity of decision-making. If there are only a few interest groups concerned by the novelty and only bilateral relations can be observed, the adoption process is comparatively simple. The more levels of a system are affected by the introduction of an innovation, the complexity of the decision-making increases as well. Regarding overcoming the barriers concerning this complexity, the expert promoter has a special significance [14].

The propensity towards innovation of promotors and other stakeholders is a crucial factor as well. It mainly depends on their respective time preference, individual risk preference and the management concept within the organizations involved. The former is largely explained by the scarceness of resources, especially financial ones. The volume of available funds for a specific period is limited. Innovations always mean an investment. Refinancing those for one occurs under high uncertainty and on the other hand impacts future business periods. Financial expenditures being invested in research, development and market introduction of innovative products reduce the volume of funds available for present consumption. Different people show differing preferences with respect to how much they are willing to invest in innovation research. The higher the willingness of all stakeholders for investments of this nature, the higher is their inclination towards innovation. Due to the high uncertainty of success, the promoters' individual risk preference is a key factor as well. Risk averse people tend to avoid uncertain investments. Consequently, people of a risk-taking nature have an encouraging effect on the innovation process. Additionally, the leadership style within the organization has an influence on the propensity to innovate. An innovation-promoting structure has a positive effect on the overall innovation process [1, 2, 7]. The groups of stakeholders have differing goals that they pursue individually. Those mostly origin from strategies within their respective institution. The individual goals of all interest groups must be identified, analysed and coordinated in order to avoid contradicting strategies and thus hindering the adoption of the novelty [9].

Due to the scarcity of resources, financial factors are of high importance. The term innovation cost includes expenses over the entire innovation process [7], i.e. expenditures for all sub-processes of research and development as well as spending on production, market introduction and sales. Throughout the entire innovation process cost emerge. Financing research and development activities, as well as determining the sales price and negotiating reimbursement with health insurers, depend on the level of total cost. The higher the cost of an innovation, the more challenging the adoption as a standard solution.

In contrast to these factors, which are mainly based on the stakeholders involved in the innovation process, stands the functionality of the existing standard of

diagnosis and treatment [14]. The more stable the current system, the less likely the successful introduction of a novelty. When initial shortcomings of the system are perceived, the first approach will always be to maintain it as much as possible. By means of compensating measures, a kind of artificial stability is created, a so-called meta-stability. Only when these are no longer sufficient, the pressure for finding alternative solutions becomes more dominant and the probability of adopting an innovation increases measurably. Thus, the innovation process proves to be risky and complex so that systematic planning in order to overcome barriers is necessary [26].

3.2.2 *Example of Application: Implant Technology*

The general model of the innovation adoption is a holistic approach that can be extended into a phase model and thereby applied to a specific case. After analysing the innovation process, the individual results can be integrated into the model. Innovative implant technology will serve as an example here for the extended adoption model (see Fig. 3.3).

Developers and manufacturers of innovative implant technology face the same challenges that become increasingly prominent in other areas of the healthcare system. Changes in the demographic structure of the population will result in a continuously altered spectrum of illnesses, i.e. predominantly older, multi-morbid patients increasingly suffering from chronic-degenerative diseases will imprint upon

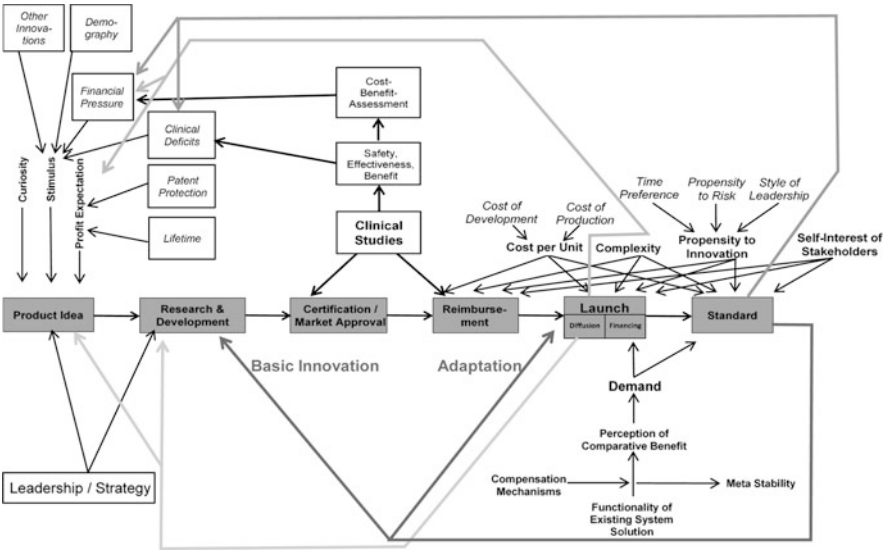

Fig. 3.3 Phase model of innovative implant technology

the range of treatment options [27]. To that regard, innovative implant technologies can contribute to an improvement in patient care [6].

In this context, researchers, developers and manufacturers of novel implant technology have to adapt to the current and future medical demand and, at the same time, anticipate and take into account challenges resulting from demographic developments. A large number of diseases of various organ systems can already be treated by using implants. Continuous research in the field of implant-based therapies should further improve and sustainably shape the treatment of these patient groups. The focus of this particular research is on the highest possible quality of life of the affected patients, even in old age [28, 29].

The model in Fig. 3.3 applies to medically relevant therapeutic concepts using innovative implant technology. The focus of development is on an improved approach to treatment compared to existing options. On the one hand, novel implants are expected to alleviate the burden on the healthcare system of treating illnesses showing a high prevalence and increasing incidence rates. In addition, implant-based treatment options are designed to improve the care of elderly, multi-morbid patients. Communication and cooperation between the numerous parties involved in the innovation process of implants is a decisive factor for the successful development and remain in the healthcare market [30]. Groups of stakeholders from different sectors are involved, either directly or indirectly. Coordinating various interest groups as well as individual objectives is crucial to the successful translation of an innovative product idea into practical application. Scientific, medical as well as economic expertise as well as the use of synergy effects thereof contribute to the accelerated adoption of innovation in the field of implant technology [28].

The adoption of innovative implants is a highly complex and multileveled process showing a large number of interdependencies [14]. In practice, the adoption process does not correspond to a linear path. It can be much rather described as an adoption cycle with multiple feedback loops [15]. The generation of a product idea initiates the subsequent steps. Upon successful adoption, the process ends with the innovative implant being established as part of the standard solution to therapy. Until finally being introduced to the market, implants pass through several phases of development. During development, new knowledge in the fields of medicine, biochemistry or engineering can be discovered that might require an early adaptation of the implant [28]. In this context, the concept of open innovation becomes increasingly relevant. This approach to innovation is defined as opening the innovation process to system elements that are not directly involved in the development and can thus significantly increase the potential of a novelty [31]. Additionally to those feedback loops, the innovation process of implant-based technologies is made up of numerous partially consecutive, partially overlapping phases; from the idea to research and implant development, market approval as well as assessment of reimbursement to the actual launch.

While the invention phase, referring to the generation of an idea, the product development and certification of a new implant, primarily represent technical problems, the latter phases of the innovation process are of an economic nature. They are shaped by cost-benefit analyses as well as the assessment of key stakeholders'

willingness to adopt. The initial phases of the portrayed process are, in contrast, characterized by clinical research, technical implementation as well as proving safety, reliability and effectiveness of the novel implant product.

The innovation cycle is determined by a number of promoters and inhibitors [2]. Process promoters are of special importance regarding implant innovation. Various legal regulations unique to the healthcare sector regulate the market for medical devices. Additionally, different markets with specific legal frameworks are attractive to implant manufacturers. These do not only differ with regard to rules on certification or market approval but also with respect to possible ways of reimbursement and regulation of competition. In this aspect, access to expertise of key people who are particularly familiar with these processes, is essential. Furthermore, *relationship promoters* are to be mentioned, who encourage and guide communication amongst the stakeholders involved [1, 18, 23].

Product Idea

The development of a product idea requires a stimulus information, curiosity and expectation of profit to coincide in the same period. This impulse can originate from another innovation, e.g. building on experience in the therapy of other organ systems or using novel materials. On the other hand, the influence of clinical deficits, like insufficiency or inadequacy of available treatment options, demographic changes associated with increasing case numbers of chronic-degenerative diseases as well as economic aspects, are displayed [32]. Curiosity and its manifestations in addition to other individual factors of the researchers strongly depend upon the style of leadership of the respective research institution. An innovation-promoting organizational structure that combines objective orientation with independence is of particular value. Besides the early estimation of cost, the expectation of profit is based on assessing possible future revenues. Other influences on the expected profit are the patent protection specifications as well as the lifetime of an implant over the product life cycle. Only the most promising product ideas are transferred to the phase of technical implementation [33].

Development

The performance of research up to the development of a prototype is a resource- and time-consuming process [15]. In general, there is a tendency that the time spent in research and development gets longer and longer while the time left for marketing opportunities of a product gets shorter and shorter. Consequently, it is highly important that the prototype is adapted to customer requirements as well as to legal requirements.

Certification and Market Approval

The CE-Certification in the European Union as well as the market approval in other countries (like the United States of America, USA) require clinical trials. Translational research from small animal models to phase III of clinical testing has a key role [15]. It aims to demonstrate effectiveness, tolerance and safety of an implant, resulting in a benefit-risk analysis [34]. Also, with regard to the options for reimbursement, clinical trials are of high importance. For the planning thereof, information on a product's market opportunities is needed at an early stage. Expected cost is compared to the benefit of an implant. The resulting cost-benefit ratio, when set compared to those of alternative therapies, can be used as an indicator for the possibility of reimbursement through statutory health insurance (SHI). In case of a negative ratio, an exit strategy can be chosen at an early stage, meaning the innovation process will be terminated and higher losses are avoided. It is of significance that the clinical trials follow a goal-oriented process as well as that leads to the innovation becoming a solution to therapy within the standard care provision.

An innovative implant mainly reaches market approval based on clinical evidence on effectiveness and safety. According to German law, a benefit assessment is currently only obligatory for medical devices of high-risk classification (§ 137 h SGB V, class III). This only partially applies to implant technology. Considering that an additional benefit for the patient is the sole reason for long-term success on the market, an early benefit assessment is essential within applying a management strategy. The problem here is that financial resources for clinical studies are not compensated by standard provision of care.

Reimbursement

Of significant importance in the entire adoption process is the possibility of reimbursement [7]. Especially in countries where the Social Health Insurance or a National Health Service covers the majority of the population (e.g. Germany and Great Britain), only those implant innovations that are reimbursable via the SHI have a chance of remaining in the market in the long run. In case of an uncertain reimbursement situation, the subsequent step of actually introducing a product to the market cannot be taken. Introduction to the market is fairly simple if the novel product is less expensive but has a similar benefit compared to the existing standard in therapy, which is already reimbursed by SHI, e.g. the case-based compensation system of the German Diagnosis Related Groups (G-DRG) [35]. Normally however, the newly developed implant will be more expensive or it will offer a therapy for a disease that has not yet been approached with an implant-based way of treatment. In those cases, a new option of refinancing must be found. The financing of implant innovations in Germany is highly restrictive, especially with regard to the hospital market. The first option of reimbursement via SHI is applied by classifying the

implant as so-called “Neue Untersuchungs- und Behandlungsmethoden (NUB)”, meaning new methods of diagnosis and treatment. Each hospital using novel implants has to apply for this individually (In Germany: § 6 Abs. 2 KHEntgG, § 135 Abs. 1 SGB V). After several years of being documented as a NUB remuneration, the product might be included into the standard care catalogue of the German SHI as an additional service or integrated into an existing DRG. Especially in the case of high-priced innovative options of treatment, it can take several years until they are included in the G-DRG catalogue [36]. The transition phase from market approval to full reimbursement represents another investment process. To ensure that the product is quickly established in the market, this process must also be thoroughly planned, guided and controlled [35].

Market Introduction and Idoption

As already shown in the general model of innovation adoption (see Fig. 3.1), the factors significantly influencing the adoption process are cost, complexity, propensity towards innovation and the self-interest of the promoters [7]. If they are not analysed early on, they can pose a barrier and hinder the adoption of novel implant technology. By applying appropriate instruments, these inhibitors can be avoided. The current situation on the market substantially determines the demand for new implants. If available treatment options sufficiently meet the medical need and do not show any clinical deficits, the demand for novel implants will be relatively low. Only when deficiencies in the current system solution are perceived, the additional benefit of innovative implant technology becomes apparent compared to other treatment options.

Feedback Loops

It is obvious that the innovation and transition process of innovative implants is complex as well as dynamic with a high level of uncertainty that must be managed strategically [26]. Even in the early stages of generating the product idea and the technical implementation thereof, the style of leadership and the choosing of an innovation strategy are highly relevant. At this point, later phases of the adoption process must already be anticipated, planned and directed. Therefore, numerous feedback loops are necessary to realize at an early stage whether an implant innovation will be successful and if not, consequently be excluded from further development. In this case, the relevant market does not only refer to the domestic one but to international ones as well. Typical feedback loops within the innovation process are [37]:

- Continuous flow of information from clinical trials concerning clinical deficits as well as cost-benefit assessments serving as stimulus for innovative product ideas.

- Continuous flow of information of cost analyses shaping profit expectations and distributing to the stimulation of necessary procedural innovation that can reduce cost.
- Continuous flow of information from the phase of launching a product on expected cost and profit possibilities.
- Continuous market research providing information on the consumer benefit, in particular for the generation of product ideas, whereby market research refers both to preferences of potential as well as actual users.
- Regularly informing product development on financing options of the potentially marketable product.
- Continuous monitoring of products established on the market in order to detect clinical deficits, the necessity of clinical studies and the pressure of cost.

Basic Innovations vs. Adaptions

In the adoption process of implant technologies, a distinction must be made between so-called basic innovations and adaptions. The former refer to novelties presenting fundamental changes based on innovative technologies [38, 39]. In a healthcare context, this refers to treatment options for diseases that could not be treated with implant-based approaches. An example is the cochlear implant that is used in the inner ear of deaf patients, be it innate or acquired. In case of successful adoption, this type of innovation passes through all phases displayed in the model, starting from the product idea until being considered a standard in medicine. In contrast, an adaption, referring to minor modifications of an existing product, does not necessarily require retaking the early steps of the innovation process [38]. Often, a re-launch is sufficient, for instance for implants using different materials or implants which can be used in another field of application.

Conclusion

It can be concluded that better clinical outcomes and improved patient care, coupled with increased cost-effectiveness compared to the current standard in therapy, are critical factors for successful adoption of novelties in the healthcare industry. The model of the innovation adoption is not only applicable to medical technologies and pharmaceutical products but also to innovative approaches to treatment and even new concepts of healthcare provision, i.e. setting up a regional cluster (e.g. “Gesundes Kinzigtal”). The statements made by the portrayed theoretical innovation model are largely valid concerning most novelties within the health sector. With the help of specific innovation analyses, many of the sub-elements of the model can be individually identified and, if necessary, further specified.

The innovation process of new treatment options starts with the very first stimulus information to innovate and, with the exception of continuous monitoring, lasts until the successful diffusion in the market of standard healthcare provision. However, patient’s access to the innovative concepts of care is often delayed. Barriers immanent over the entire innovation process are the main reason for this. To ensure a

Fig. 3.4 Determining factors of innovation management in healthcare

successful translation, it is essential to raise the awareness of all relevant interested groups concerning obstacles to adoption.

Figure 3.4 shows the core factors shaping the management of novelties in the field of healthcare. Innovation management is necessary due to scarcity of resources and the legal framework of the healthcare sector amongst other factors. The innovation process is further categorized by the existence of specific inhibitors and promoters. All processes of planning, controlling, managing and communication are in the focus of innovation management. Especially, tools of communication are of high relevance in the healthcare industry because it is shaped by a large number of stakeholders. One of the core responsibilities of innovation management is the coordination of partially differing interests during the decision-making processes around the introduction and application of an innovative concept of healthcare provision.

The healthcare sector in general is facing a steadily increasing pressure to innovate. Continuously progressing research and the resulting additional medical and technical knowledge are only some of the reasons for this development. This provides many new opportunities for suppliers of healthcare services. The spectrum of technically feasible treatment methods is widening. On the other hand, the allocation of ever-scarce financial resources will have a decisive impact on both research and healthcare provision. Throughout the entire process of research and development, financing must be ensured, especially in the case of technically and medically challenging concepts. Investments in futile concepts should be ruled out as early as possible. Financial resources for reimbursement in the healthcare market are also limited and will become even scarcer in the future. Merely care concepts and

therapeutic approaches that greatly benefit large parts of the population will remain on the market in the end [27].

Demographic change is one of the factors responsible for the scarcity in resources. Even today, its impact on healthcare is already clearly noticeable. A change in the spectrum of diseases is the consequence of an ageing population. The demand for options in diagnosis and therapy that show a positive impact on the overall health status as well as on the health-related quality of life into old age will increase. Innovative care concepts that, on the one hand, can counteract the impending scarcity of qualified personnel, especially in rural areas and, on the other hand, ensure comprehensive healthcare provision for an ageing society, will continue to gain importance in the future [15, 27].

This means building a holistic innovation management right from the early phases is key. For one, this serves to utilize available resources in the most efficient way possible. On the other hand, it increases the probability of adoption. The capability of rapidly adopting new concepts of production and being able to adapt to a changing market is of great importance. These factors contribute to increasing attractiveness, maintaining competitiveness and ultimately aiming for sustainability of innovative concepts of care.

Take Home Message

- The development of an innovative product from the first idea to a standard device or practice is a complex process of different interrelated phases and requires several feedback loops.
- The successful adoption of an innovation requires different promoters: an expert promoter overcomes the barrier of "not-knowing"; a hierarchical promoter defeats the resistance of "not-liking"; a process promoter helps to reduce the barrier of administration; a relationship promoter is steadily seeking for innovations.
- Systemic innovation management from the early initiation until the launch of the new product and finally to a steady process of adaption is a prerequisite of effective and efficient development of new products.
- An early analysis of market chances is the key to successful innovation development.
- Expected costs and revenues are most important factors influencing the development process. Cost analysis is crucial even in countries where regulatory processes do not require them officially, as they are essential to estimate future return on investment.

References

1. Hauschildt J et al (2016) Innovations management. Vahlen, München
2. Vahs D, Brem A (2015) Innovationsmanagement: Von der Idee zur erfolgreichen Vermarktung, 4th edn. Schäffer-Poeschel Verlag, Stuttgart

3. Corsten H et al (2017) Grundlagen des Technologie-und Innovationsmanagements, 2nd edn. Franz Vahlen, München
4. Trott P (2012) Innovation management and new product development, 5th edn. Pearson Education, Harlow
5. Fleßa S (2006) Helfen hat Zukunft: Herausforderungen und Strategien für karitative und erwerbsorientierte Sozialleistungsunternehmen. Vandenhoeck & Ruprecht, Göttingen
6. e.V. BM (2017) CE-Kennzeichnung. https://www.bvmed.de/de/recht/ce-kennzeichnung
7. Fleßa S (2014) Grundzüge der Krankenhausbetriebslehre, 2nd edn. Oldenbourg, München
8. Bührlen B (2008) Innovationssystem Gesundheit: Ziele und Nutzen von Gesundheitsinnovationen. Fraunhofer-IRB-Verlag, Stuttgart
9. Heyen NB, Reiß T (2014) Das Gesundheitswesen aus Innovationssystemperspektive: Acht Thesen und Handlungsmöglichkeiten: Teil 1. Sozialer Fortschritt 63:245–252
10. Ritter W (1991) Allgemeine Wirtschaftsgeographie. Oldenbourg, München
11. Fleßa S, Marschall P (2012) Individualized medicine: from niche position to macro innovation. Pharmacoecon German Res Articles 10(2):53–67
12. Thom N (1980) Grundlagen des betrieblichen Innovationsmanagements. Peter Hanstein Verlag, Königstein
13. Disselkamp M (2017) Innovationen und Veränderungen. Kohlhammer Verlag, Stuttgart
14. Fleßa S, Greiner W (2013) Grundlagen der Gesundheitsökonomie: eine Einführung in das wirtschaftliche Denken im Gesundheitswesen, 3rd edn. Springer Gabler, Berlin
15. Beyar R (2015) The long and winding road to innovation. Rambam Maimonides Med J 6(3):598–604
16. Mirow C (2010) Innovationsbarrieren. Springer, Wiesbaden
17. Goduscheit RC (2014) Innovation promoters—a multiple case study. Ind Mark Manag 43(3):525–534
18. Witte E (1973) Organisation für Innovationsentscheidungen: Das Promotoren-Modell. Schwartz, Göttingen
19. Gemünden HG, Salomo S, Hölzle K (2007) Role models for radical innovations in times of open innovation. Creat Innov Manag 16(4):408–421
20. Hausschildt J, Chakrabati A (1988) Arbeitsteilung im Innovationsmanagement-Forschungsergebnisse, Kriterien und Modelle. Zeitschrift Führung+Organisation 57:378–388
21. Hauschildt J, Schewe G (2000) Gatekeeper and process promotor: key persons in agile and innovative organizations. Int J Agil Manag Syst 2(2):96–103
22. Gemünden H, Salomo S, Hölzle K (2007) Role models for radical innovations in times of open innovation. Creat Innov Manag 16(4):408–421
23. Der Walter A (1998) Beziehungspromotor: Ein personaler Gestaltungsansatz für erfolgreiches Relationship Marketing. Springer, Wiesbaden
24. Hirzel M, Kühn F, Gaida I (2013) Prozessmanagement in der Praxis: Wertschöpfungsketten planen, optimieren und erfolgreich steuern, 3rd edn. Gabler Verlag, Wiesbaden
25. Fleßa S (2002) Gesundheitsreformen in Entwicklungsländern: eine kritische Analyse aus Sicht der kirchlichen Entwicklungshilfe. Lembeck, Frankfurt am Main
26. Auffermann S, Der Staudt E (1999) Innovationsprozess im Unternehmen—eine erste Analyse des derzeitigen Stands der Forschung. IAI, Bochum
27. Kickbusch I (2006) Die Gesundheitsgesellschaft: Megatrends der Gesundheit und deren Konsequenzen für Politik und Gesellschaft. Verlag für Gesundheitsförderung, Hamburg
28. Faulkner A, Kent J (2001) Innovation and regulation in human implant technologies: developing comparative approaches. Soc Sci Med 53(7):895–913
29. Response K (2017) Gemeinsam Zukunft gestalten. http://www.response.uni-rostock.de/
30. Nienaber A-M (2011) Markteinführung von Produktinnovationen in der Medizintechnik: eine empirische Untersuchung zur Ausgestaltung des Kommunikations-Mix. Duncker & Humblot, Berlin
31. Chesbrough HW (2003) Open innovation: the new imperative for creating and profiting from technology. Harvard Business Press, Boston

32. Strech D (2011) Priorisierung und Rationierung im Gesundheitswesen-Status quo und Perspektiven. In: Hensen P, Kölzer C (eds) Die gesunde Gesellschaft. Springer, Wiesbaden, pp 51–61
33. Verworn B, Herstatt C (2001) Managing the fuzzy front end of innovation. Technical University of Hamburg, Hamburg
34. Volk N, Klüß C (2010) Klinische Studien von Medizinprodukten: Übersicht und Ausblick der aktuellen Gesetzgebung und Normen. Kardiotechnik 1(19):12–19
35. Cappellaro G, Ghislandi S, Anessi-Pessina E (2011) Diffusion of medical technology: the role of financing. Health Policy 100(1):51–59
36. GKV-Spitzenverband (2017) Neue Untersuchungs- und Behandlungsmethoden (NUB). https://www.gkv-spitzenverband.de/krankenversicherung/krankenhaeuser/drg_system/neue_untersuchungs_und_behandlungsmethoden_nub/neue_untersuchungs_und_behandlungsmethoden_nub.jsp
37. Kline S, Rosenberg N (1989) An overview of innovation. In: Landau R, Rosenberg N (eds) The positive sum strategy—harnessing technology for economic growth. National Academy Press, Washington, DC
38. Dosi G (1988) Sources, procedures, and microeconomic effects of innovation. J Econ Lit 26(3):1120–1171
39. Pfeiffer W et al (1997) Funktionalmarkt-Konzept zum strategischen Management prinzipieller technologischer Innovationen, 28th edn. Vandenhoeck & Ruprecht, Göttingen

Sources of Law

Gesetz über die Entgelte für voll- und teilstationäre Krankenhausleistungen (KHEntgG), Date: 23.04.2002: § 6 Vereinbarung sonstiger Entgelte Abs. 2

Gesetz zur Neuordnung des Arzneimittelmarktes in der gesetzlichen Krankenversicherung (AMNOG), Date: 22.12.2010: Artikel 1 Absatz 5

Sozialgesetzbuch Fünftes Buch – Gesetzliche Krankenversicherung (SGB V), Date: 20.12.1988: § 135 Bewertung von Untersuchungs- und Behandlungsmethoden

Sozialgesetzbuch Fünftes Buch – Gesetzliche Krankenversicherung (SGB V), Date: 20.12.1988: § 137h Bewertung neuer Untersuchungs- und Behandlungsmethoden mit Medizinprodukten hoher Risikoklasse

Part II
Definitions and Regulations

Chapter 4
Definition and International Regulations for Medical Devices

Eugenio Mattei, Federica Censi, and Giovanni Calcagnini

Abstract The term medical device refers to a wide variety of products. They range from simple low-risk devices such as stethoscopes and syringes, through imaging device and in vitro diagnostic, up to high-risk biocompatible implants, such as orthopaedic prostheses and pacemakers.

The number and variety of medical devices are increasing as new software and hardware applications, new materials and new combination products are developed and to classify these according to the intended purpose and the different options may be a difficult task.

The identification of a product as a medical device and the further classification into classes of risk is the base for the application of the correct regulatory path worldwide, although differences exist at national level in such classifications.

The development of consistent, harmonized definitions for the terms "medical device" and "in vitro diagnostic medical device" would offer significant benefits to the manufacturer, user, patient and to regulatory authorities. This can also support the global convergence of regulatory systems.

This chapter aims to give a comprehensive description of the different regulations concerning the medical devices worldwide with special reference to the EU Medical Device Directive. The role and importance of the technical standards are also described.

Introduction

More than 20,000 types of medical devices now exist. They range from simple low-risk devices such as stethoscopes and syringes, through imaging device and in vitro diagnostic, up to high-risk biocompatible implants, such as orthopaedic prostheses and pacemakers.

The number and variety of medical devices are increasing as new software and hardware applications, new materials and new combination products are developed

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and to classify these according to the intended purpose and the different options may be a difficult task.

The identification of a product as a medical device and the further classification into classes of risk is the base for the application of the correct regulatory path worldwide, although differences exist at national level in such classifications.

The development of consistent, harmonized definitions for the terms "medical device" and "in vitro diagnostic medical device" would offer significant benefits to the manufacturer, user, patient or consumer, and to regulatory authorities and support global convergence of regulatory systems.

An attempt to develop a consistent, harmonized definition for the terms "medical device", and an "in vitro diagnostic medical device", has been carried out by The Global Harmonization Task Force of the World Health Organization.

The goals of the Global Harmonization Task Force (GHTF) go beyond proposing definitions, since also include standardizing of nomenclature for defining and naming innovative technologies, classifying the devices for regulatory approval (registration) and encouraging convergence in the evolution of regulatory systems for medical devices in order to facilitate trade whilst preserving the right of participating members to address the protection of public health by those regulatory means considered the most suitable. The final goal is to have an international classification, coding and nomenclature for medical devices that would be accepted and used worldwide.

4.1 The Medical Device Concept and Classification

The term "medical device" covers a very wide range of products, such as instruments, software and materials (i.e. substances). Although the definitions of medical device may differ among national legislations, most of the definitions are based upon two principles:

1. The medical purpose: A medical device is intended to be used to diagnosis, prevention, monitoring, treatment or alleviation of a disease or injury,
2. The mechanism of action: The principal mechanism of action of a medical device should not be based on pharmacological, immunological or metabolic mechanisms.

The medical purpose differentiates medical devices from everyday devices, whereas the mechanism of action differentiates medical devices from pharmaceutical products.

The adoption of these two principles is reflected in the definitions proposed in 2012 by the Global Harmonization Task Force:

> *A medical device is an article, instrument, apparatus or machine (including mobile medical applications and software) that is intended by manufacturer to be used alone or in combination in the prevention, diagnosis or treatment of illness or disease, or for detecting, measuring, restoring, correcting or modifying the structure or function of the body for some*

health purpose. Typically, the purpose of a medical device is not achieved by pharmacological, immunological or metabolic means.

A subset of medical devices, defined as devices which, whether used alone or in combination, are intended by the manufacturer for the examination in vitro of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes. They include reagents, calibrators, control material and test kits. [1]

The classification of medical devices is a "risk-based" system based on the vulnerability of the human body taking account of the potential risks associated with the devices. This approach allows the use of a set of criteria that can be combined in various ways in order to determine classification, e.g. duration of contact with the body, degree of invasiveness and local vs. systemic effect. These criteria, also referred to as "classification rules" have been object of a proposal from the Global Harmonization Task Force (GHTF) [2]. The proposal of the GHTF introduces a device classification system consisting of four classes where Class A represents the lowest hazard and Class D the highest.

Although these proposals have not yet been formally adopted at national levels, the definitions and classification rules found in the regulatory frameworks of the major markets (i.e. Europe, United States and Japan) are consistent with the definitions and classification rules laid down by the Global Harmonization Task Force.

4.1.1 Definition of Medical Device in Europe

For the European Market, the definition of medical device was originally given in Article 2 of the Council Directives 90/385/EEC [3], 93/42/EEC on medical devices (Medical Device Directive—MDD) [4], and then amended in the Directive 2007/47/EEC (mostly to include stand-alone software products) [5]. The new released Regulation 2017/745 on Medical Device (Medical Device Regulation—MDR) [6] has further modified the definition to include the "in vitro" diagnostic medical device:

"Medical device" means any instrument, apparatus, appliance, software, implant, reagent, material or other article intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the following specific medical purposes:

- *diagnosis, prevention, monitoring, prediction, prognosis, treatment or alleviation of disease,*
- *diagnosis, monitoring, treatment, alleviation of, or compensation for, an injury or disability,*
- *investigation, replacement or modification of the anatomy or of a physiological or pathological process or state,*
- *providing information by means of in vitro examination of specimens derived from the human body, including organ, blood and tissue donations, and which does not achieve its principal intended action by pharmacological, immunological or metabolic means, in or on the human body, but which may be assisted in its function by such means.*

The following products shall also be deemed to be medical devices:

- *devices for the control or support of conception;*
- *products specifically intended for the cleaning, disinfection or sterilization of devices as referred to in Article 1(4) and of those referred to in the first paragraph of this point.*

Thus, as mentioned above, a product will be considered to fall within the definition of a medical device if it has a medical purpose and if the product functions primarily in a way that is not metabolic, immunological or pharmacological. The determination of whether a product is considered to have a medical purpose will be based on the intended purpose declared by the manufacturer.

The cases where it is not clear whether a product is a medical device, fall within the competence of the Competent Authorities of the Member States where the product is on the market. However, to help in the decision, the European Commission has published and keeps updated a Manual on Borderline and Classification in the Community Regulatory Framework for Medical Devices [7].

Once a product meets the criteria to be considered a medical device, a further distinction between medical device and "in vitro" medical device has to be made. This distinction has an impact on the regulatory path to be followed for put the product into the European Union (EU) market.

For a medical device, a further distinction between "Active Implantable Medical Device" and "Medical Device" has to be made. Finally, for (not-Active Implantable) medical device a class of risk (I, Is, Im, IIa, IIb or III) has to be assigned. Classification rules were laid down in Annex IX of MDD and are now laid down in Annex VIII of MDR. The document "MEDDEV 2. 4/1-classification of medical devices" provides a practical guide and examples to rule interpretation and application [8]. A more detailed examination of the risk classes will be given in the following paragraphs dedicated to regulations and directives.

4.1.2 Definition of Medical Device in the United States

For the US market, the definition of a medical device is given in section 201(h) of the Federal Food Drug & Cosmetic (FD&C) Act [9]. A device is:

an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

1. *recognized in the official National Formulary, or the United States Pharmacopoeia (USP), or any supplement to them,*
2. *intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or*
3. *intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. The term "device" does not include software functions excluded pursuant to section 520(o).*

If a product is labelled, promoted or used in a manner that meets the above definition, it will be regulated by the Food and Drug Administration (FDA) as a

medical device and is subject to premarketing and post-marketing regulatory controls, according to its class of risk (I, II or III).

In cases where it is not clear whether a product is a medical device, the Center for Device and Radiological Health (CDRH) of FDA has established and maintains a public classification database [10] which contains products FDA considers devices and the associated codes developed to support its regulatory and administrative processes. In addition, if the preceding information does not result in determining whether a product is a device, the Centre's Device Determination Officers, Office of Compliance, may be contacted.

4.1.3 Definition of Medical Device in Japan

For the Japanese market, the definition of medical device was originally laid down in the Japan's Pharmaceutical Affairs Law (PAL). The intent of PAL was to harmonize requirements by incorporating the guidance documents of the Global Harmonization Task Force (GHTF). This includes quality management systems (QMS) requirements based on the ISO 13485 norm.

Article 2, Paragraph 4, of the Pharmaceutical Affairs Law defines medical devices as "*instruments and apparatus intended for use in diagnosis, cure or prevention of diseases in humans or other animals; intended to affect the structure or functions of the body of man or other animals*" [11].

Pharmaceutical Affairs Law (PAL) was replaced in 2014 by the Pharmaceuticals and Medical Devices Act (PMD Act), also known as the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The definition of medical device was not changed, but in the text is further specified that the term "medical device" refers to: *any instruments, machines, apparatus, materials, software, reagent for in vitro use, and other similar or related articles, which is used in diagnosing, curing, alleviating, or directly preventing human diseases, regulating fertility, or which may affect the body structure or functions of human beings, and do not achieve its primary intended function by pharmacological, immunological or metabolic means in or on the human body* [12].

Under Japan PMDA regulations, a medical device can be classified, as a General Medical Device (Class I), Controlled Medical Device (Class II) or a Specially Controlled Device (Class III and Class IV), depending on the risk level.

4.2 Regulations (EU, USA, Japan)

Despite global efforts to harmonize regulation of medical devices via groups such as the Global Harmonization Task Force (GHTF), and the International Medical Device Regulators Forum there is a huge discrepancy among regulatory requirements all over the world.

The differences lie not only in the classification of devices, but also in the overall process, the quickness of approvals, their applicability across regions and the expense involved, although it is acknowledged worldwide that a global approach to auditing and monitoring the manufacturing of medical devices could improve their safety and oversight on an international scale.

The three main regulatory frameworks are: the CE-Mark, the US-FDA approval, and the Japanese PMDA. Each of them differs in the aim of the regulation and in the process involved. CE-marking was established mainly to guaranty the safety of the device, as a requisite for the free commercialization in all the EU Countries. The US FDA also focuses on safety but with the additional requirement of evaluating the efficacy. Japanese PMDA looks to quality, efficacy and safety.

4.2.1 European Regulatory Framework: CE-Mark

Medical devices, as many other products, require CE-marking before they can be sold in the European Economic Area (EEA). CE-marking proves that the device has been assessed and meets EU safety, health and environmental protection requirements. It is valid for devices manufactured both inside and outside the EEA, that are then marketed inside the EEA.

The EU-wide requirements are laid down in directives or regulations that cover different products or product sectors. For medical devices, the relevant directives were adopted more than 25 years ago and represented a significant change for manufacturers and competent authorities:

- Directive 90/385/EEC regarding active implantable medical devices (AIMDD)
- Directive 93/42/EEC regarding medical devices (MDD)
- Directive 98/79/EC regarding in vitro diagnostic medical devices (IVDD)

Based on the data collected, and on the experience gained during these years of application, the Directives were amended in 2010 (Directive 2007/47/EC).

In 2017, the Directives have been superseded by the adoption of the Regulation (EU) 2017/745 on Medical Devices (MDR) and Regulation (EU) 2017/746 on In Vitro Diagnostic Devices Regulation (IVDR). A “Regulation” (unlike a Directive) is directly applicable as a law and has consistent effect in all EU Member States.

The EU's Medical Device Regulation (MDR) was officially published on 5 May 2017 and came into force on 25 May 2017. The MDR will replace the EU's current Medical Device Directive (93/42/EEC) and the EU's Directive on active implantable medical devices (90/385/EEC).

From 26 May 2020, new devices will have to meet the requirements of the MDR in order to be placed in the European market.

Devices holding a certificate from a European Notified Body under either the Medical Device Directive (93/42/EEC) or the Active Implantable Medical Devices Directive (90/385/EEC) have an additional grace period and may continue to be placed on the market until 26 May 2024 if the manufacturer fulfil the specific prerequisite requirements drawn in the MDR.

Due to the COVID-19 outbreak, the application of MDR have been postponed by a year in a bid to prevent shortages in getting key equipment on the market during the coronavirus pandemic. The Medical Devices Regulation (MDR) was due to be enforceable on 26 May 2020 but will now take effect on 26 May 2021.

Fig. 4.1 Calendar for the introduction of the MDR application

The MDR provides for a transition period of 3 years and fully applies on 26 May 2020.[1] The IVDR provides for a transition period of 5 years and will fully apply from 26 May 2022. During the transition period, manufacturers can place devices on the market under the currently applicable EU Directives (93/42/EEC, 98/79/EC and 90/385/EEC) or under the new Regulation. Due to the COVID-19 pandemic, an amendment to the MDR was adopted on 24 April 2020 by European Commission, which postponed the application of most of its provisions by 1 year, until 26 May 2021. The European Commission considered such a delay necessary given that the public health crisis has created a demand for substantial additional resources and medical devices of vital importance, such as medical gloves, surgical masks, equipment for intensive care and other medical equipment, which could not have been reasonably anticipated at the time of adoption of the MDR (see summary in Fig. 4.1).

For medical devices and active implantable medical devices, the technical requirements are detailed in Annex I of each of the MDD and AIMDD. These requirements are called Essential Requirements (ER). There are 13 ERs in the MDD and 16 in the AIMDD. The General Safety and Performance Requirements (SPRs) listed in Annex I of MDR have replaced the Essential Requirements. The scope and topics are consistent overall with the ERs of the Directives. However, there are a few notable differences.

For some medical devices, other regulations may be also applicable: the Restriction of Hazardous Substances (RoHS) Directive, the General Data Protection Regulation (GDPR) or the Machinery Directive since those requirements are more specific than the essential requirements set out in Annex I to the MD or AIMD

[1] Status May 2021: the full application of MDR has been postponed for organizational reasons.

Directives or MDR. In other cases (e.g. Low Voltage Directive and Electromagnetic Compatibility Directive) since the prescriptions of the Medical Device Directives/Regulation are more restrictive, there is no requirement to demonstrate the compliance with these Directives.

It is up to the manufacturer to make sure that the product meets all the EU legal requirements. Unless the device is a low-risk device, special conformity assessment bodies ("Notified Bodies") must verify that the specific technical requirements are met. The conformity assessment usually involves an audit of the manufacturer's quality system and, depending on the type of device, a review of technical documentation from the manufacturer on the safety and performance of the device.

Thus, in order to choose the proper certification path, the medical device shall be **classified** according to the class of risk laid down in the respective Directive/Regulation.

4.2.2 CE-Mark Device Classification

According to the European framework, there are four classes of medical devices: Class I, IIa, IIb and III. The medical devices of Class III hold the highest risk.

The classification rules are laid down in Annex IX of the MDD Directive (Annex VIII of the MDR). A guideline to classification can be found in document MEDDEV 2.4/1 [8].

- **Class I** Medical Devices: Medical devices class I have the lowest perceived risk. Several non-invasive, non-active devices belong to this class (e.g. plasters, scalpels, otoscopes, wheelchairs. . .). This class has also two subclasses: "**Is**" if the medical device is sterile, e.g. a personal protection kit; "**Im**" if the medical device has measuring functions, e.g. stethoscope.
- **Class IIa** Medical Devices: This class includes several active diagnostic and therapeutic devices such as hearing aids, diagnostic ultrasound machines, ECG and EEG devices, etc. They usually constitute low- to medium-risk. Patients should use them for a short-term period, any less than 30 days.
- **Class IIb** Medical Devices: It include medical devices such as long-term corrective contact lenses, surgical lasers, defibrillators and others. They are medium- to high-risk devices, and patients may use them for a period longer than 30 days.
- **Class III** Medical Devices: In that class, all medical devices have the highest risk possible. Such devices are, for instance, cardiovascular catheters, aneurysm clips, hip-joint implants, prosthetic heart valves and others.

No classes of risk are defined for active implantable devices (e.g. pacemakers, implantable cardioverter defibrillators, cochlear implants implantable nerve stimulators), since these devices are regulated by their own directive (AIMD). In the MDR, AIMD related devices will be classified as Class III.

In the near future, due to the stricter rules of the new Regulation (MDR), the class of some devices may change (e.g. up-classification of some stand-alone software products, up-classification of external defibrillators).

4.2.3 Major Changes Introduced by the MDR

Even if MDR is not radically different from MDD, additional work will be required to companies who want to continue supplying their devices beyond 2020. Most of the new requirements are extensions to already existing requirements. The current four classes I, IIa, IIb and III are retained without change, and the classification rules are mostly the same, with some changes related to substances, up-classification of software and of some specific devices. The essential requirements are still listed in Annex 1 of the MDR, are now renamed as "general requirements" and have been extended. All medical devices that incorporate electronic programmable systems and software or that are medical devices in themselves shall be developed and manufactured in accordance with the state of the art taking into account the principles of risk management, including information security, as well as to set out minimum requirements concerning IT security measures, including protection against unauthorized access.

The manufacturers may choose among different certification routes, but with fewer options than before.

The requirements related to post-market surveillance (PMS) have been expanded. The MDR defines post-market surveillance as a proactive and systematic process which manufacturers implement and carry out (with other economic operators) in order to take corrective and preventive action (CAPA) in accordance with information on medical devices and their performance. Companies have to institute and keep up to date a systematic procedure to collect and review experience gained from devices they place on the market and produce a PMS Report or, depending on the device class, a Periodic Safety Update Report (PSUR). The aim of the post-market surveillance system is to actively and systematically gather, record and analyse relevant data on the quality, performance and safety of a device throughout its entire lifetime. This allows manufacturers to continuously update the risk-benefit assessment and to initiate necessary measures without delay. Manufacturers are obliged to collect and assess all information about their medical devices and related devices from competitors.

MDR requires manufacturers to prepare and implement a post-market surveillance plan (Article 84), which is part of the technical documentation and proves compliance with the PMS requirements of the MDR. Annex III specifies the requirements and the content of such a post-market surveillance plan, and covers at least:

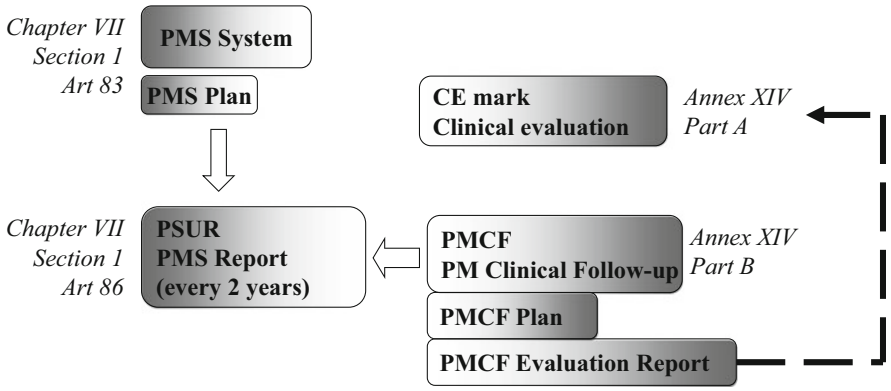

Fig. 4.2 Relation among the Post-Market Clinical Follow-up (PMCF), the post-market surveillance (PMS) plan and Periodic Safety Update Report (PSUR)

- *a proactive and systematic process to collect any information referred to in point (a). The process shall allow a correct characterization of the performance of the devices and shall also allow a comparison to be made between the device and similar products available on the market.*
- *effective and appropriate methods and processes to assess the collected data.*
- *suitable indicators and threshold values that shall be used in the continuous reassessment of the benefit-risk analysis and of the risk management as referred to in Section 3 of Annex I.*
- *effective and appropriate methods and tools to investigate complaints and analyse market-related experience collected in the field.*
- *methods and protocols to manage the events subject to the trend report as provided for in Article 88, including the methods and protocols to be used to establish any statistically significant increase in the frequency or severity of incidents as well as the observation period.*
- *methods and protocols to communicate effectively with competent authorities, notified bodies, economic operators and user.*
- *reference to procedures to fulfil the manufacturers obligations laid down in Articles 83, 84 and 86.*
- *systematic procedures to identify and initiate appropriate measures including corrective actions.*
- *effective tools to trace and identify devices for which corrective actions might be necessary.*
- *a Post-Market Clinical Follow-up (PMCF) plan as referred to in Part B of Annex XIV, or a justification as to why a PMCF is not applicable.*

The relation among the PMCF, the PMS plan and PSUR is depicted in Fig. 4.2. MDR has introduced the Unique Device Identification (UDI). The UDI is a series of numeric or alphanumeric characters that is created through a globally accepted device identification and coding standard. It allows the unambiguous identification of a specific device on the market. Although UDI is a new requirement in Europe, it has been an established requirement in the United States.

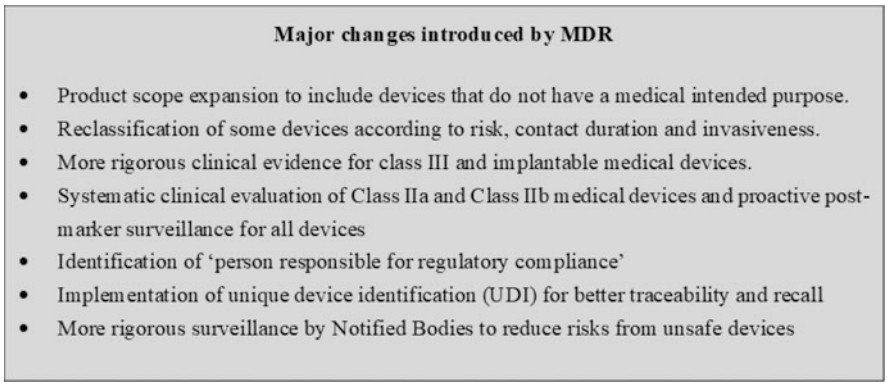

Fig. 4.3 Major changes introduced by the MDR

There are two requirements in the MDR which are novel (see also Fig. 4.3):

- Company shall appoint at least one person responsible for ensuring the regulatory compliance (the requisite expertise this person should have are laid down in Article 15).
- The extension of the scope of the medical device regulations to products without an intended medical purpose but which are analogous to devices with a medical purpose. This is aimed at medical device like products typically intended for cosmetic purposes (e.g. coloured non-corrective contact lenses). Annex XVI of MDR contains a list of groups of such products.

4.2.4 CE-Mark Certification and Declaration of Conformity

According to the European framework, if a medical device is in any other class apart from class I, a Notified Body assessment is required that the medical device fulfils the essential requirements of the respective CE directives.

For medical devices belonging to class IIa, IIb or III medical device, the declaration of compliance (CE Declaration) will have to be backed up with a Notified Body assessment (CE Certificate). Only then, the product can be placed on the market. The conformity assessment of the medical devices by the Notified Body may include an audit of the technical documentation and a quality system/product inspection, and to be focused on one or more aspects of the device design and production as summarized in Table 4.1.

The conformity assessment may follow different procedures, as listed in Annexes II, III, IV, V and VI of the MDD Directive. MDR has reduced the certification routes options, which are now listed in Annex IX to XI [6].

Table 4.1 Notified body assessment for CE certificate

Device class	Notified body (CE certificate)	Note
Class I	Not required	Manufacturer self-declaration
Class Is, Im	Required	Assessment by the Notified Body limited to measurement and sterilization issues
Class IIa	Required	Assessment of design/project by Notified Body not required Assessment of specific procedures of the Quality Management System by the Notified Body
Class IIb	Required	Assessment of Technical Documentation and of Quality Management System by the Notified Body
Class III and active implantable devices	Required	Assessment of Technical Documentation and Quality Management System by the Notified Body

4.3 US Regulatory Framework: FDA Notification and Approval

Medical devices marketed in the United States are subject to the regulatory controls in the Federal Food, Drug, and Cosmetic Act (FD&C Act) and the regulations in Title 21—Code of Federal Regulations [9].

The regulatory process with FDA is mainly based on the equivalence principle. The philosophy of this process involves proving substantial equivalence between the new device and the predicate (legally marketed) device, rather than an independent demonstration of the new device safety and effectiveness. The substantial equivalence should be not only in terms of technological and design characteristics but also on performance data and should have same intended use as the predicate device. If substantial equivalence cannot be established, the device generally requires premarket approval (PMA).

The first step in preparing a device for marketing is to classify the device. A medical device is defined by law in the section 201(h) of the FD&C Act, and the classification, which may be found in the Code of Federal Regulations, determines the regulatory path and regulatory requirements for your device, i.e. the type of premarketing submission/application required for FDA clearance to market. The marketing pathways include Premarket Notification (510(k)), De Novo Classification Request, Exempt, Premarket Approval (PMA), Product Development Protocol (PDP), Humanitarian Use Exemption (HDE) and Biologics License Application (BLA).

4.3.1 FDA Device Classification

Device classification depends on the intended use of the device and upon indications for use. Indications for use can be found in the device's labelling but may also be

conveyed orally during sale of the product. A discussion of the meaning of intended use is contained in the 510(k) Programme: "Evaluating Substantial Equivalence in Premarket Notification" (510(k)). In addition, classification is risk based, that is, the risk the device poses to the patient and/or the user is a major factor in the class it is assigned. Class I includes devices with the lowest risk and Class III includes those with the greatest risk.

The Food and Drug Administration (FDA) has established classifications for approximately 1700 different generic types of devices and grouped them into 16 medical specialties referred to as panels. Each of these generic types of devices is assigned to one of three regulatory classes based on the level of control necessary to assure the safety and effectiveness of the device.

4.3.2 FDA Premarket Approval and Premarket Notification Process

The class to which your device is assigned determines, among other things, the type of premarketing submission/application required for FDA clearance to market. If your device is classified as Class I or II, and if it is not exempt, a 510k will be required for marketing. For Class III devices, a premarket approval application (PMA) will be required.

As indicated in Table 4.2, all classes of devices are subject to General Controls. General Controls are the baseline requirements of the Food, Drug and Cosmetic (FD&C) Act that apply to all medical devices, Class I, II and III.

Premarket Approval (PMA) application is a scientific, regulatory documentation to FDA to demonstrate the safety and effectiveness of the class III device. There are administrative elements of a PMA application, but good science and scientific writing is a key to the approval of PMA application.

A 510(k) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to an

Table 4.2 Regulatory controls required by FDA

Device class	Regulatory controls	Notification/ approval	Note
Class I	General controls	510k premarket notification	Unless exempted
Class II	General controls and special controls	510k premarket notification	Unless exempted
Class III	General controls and premarket approval	Premarket approval application (PMA)	Unless your device is a pre-amendments device (on the market prior to the passage of the medical device amendments in 1976, or substantially equivalent to such a device) In that case, a 510k will be the route to market

already legally marketed device that is not subject to PMA. The 510(k) notification should include a physical description of the new device, together with an explanation of its intended use, principles of operation, power source, composition, and other information necessary to understand the device.

4.4 Japanese PMDA

Japan's Ministry of Health, Labour and Welfare (MHLW) is the regulatory body that oversees food and drugs in Japan, which includes creating and implementing safety standards for medical devices and drugs. In conjunction with the MHLW, the Pharmaceutical and Medical Device Agency (PMDA) is an independent agency that is responsible for reviewing drug and medical device applications. The PMDA works with the MHLW to assess new product safety, develop comprehensive regulations and monitor post-market safety.

Medical devices are regulated by the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (hereinafter referred to as "the Pharmaceuticals and Medical Devices Act"), which came into effect in November 2014.

Medical Devices are classified by risk base concept, into four classes. All devices shall be in conformity with the Essential Principles (Eps). Essential Principles are revised according to the GHTF document on Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices [13].

4.4.1 Japan Medical Device Classification

Under Japan PMDA regulations, a medical device can be classified as a General Medical Device (Class I), Controlled Medical Device (Class II) or a Specially Controlled Device (Class III and Class IV), depending on the risk level. A summary is given in Table 4.3.

For General Medical Devices, only a notification/self-declaration is required, and the product does not need to undergo the approval process by the MHLW and PMDA.

Controlled Medical Devices can be designated to be certified by an authorized third-party certification entity or reviewed by the Pharmaceutical and Medical Device Agency (PMDA).

Specially Controlled Medical Devices must be reviewed and approved by the PMDA and Ministry of Health, Labour and Welfare (MHLW).

Table 4.3 Classification and regulation regarding medical devices in Japan

GHTF classification	Category	Regulatory requirements		
Class A	Extremely low risk e.g. X-ray film	General MDs (Class I)	Self-declaration: approval of the product is not required, but marketing notification is necessary	
Class B	Low risk e.g. MRI, digestive catheters	Controlled MDs (Class II)	Third-party Certification: Certification by a registered certification body is required	Minister's Approval (Review by PMDA) The Minister's approval for the product is required
Class C	Medium risk e.g. dialyzer	Specially Controlled MDs (Class III & IV)		
Class D	High risk e.g. pacemaker		Minister's Approval (Review by PMDA) The Minister's approval for the product is required	

4.4.2 PMDA Process

The Japanese approval process is essentially the approval of two aspects:

- Device: This involves review against Essential Principles (EP) and Summary Technical Documentation (STED) data subsets. EPs are specified in "the Standards for medical devices" as stipulated by the Japanese law. EPs cover design and manufacture (toxicity, compatibility, hardness, wear and degree of fatigue, handling, etc.), risk management, performance and function, durability, transport and storage and benefits of device. The Summary Technical Documentation for Demonstrating Conformity to the Essential Principles of Safety and Performance of Medical Devices (STED) is a practical method to harmonize device regulation and bring Japan in line with other international regulatory bodies. Similar in principle to FDA 510(k) it attempts to show equivalence of a new device with a predicate device. It attempts to develop a common regulatory format for all the major regulatory bodies.
- Manufacturing facilities: data reliability, GLP, GCP, GMP conformity, post-approval inspection.

Each device is reviewed depending on its specific risk:

1. For review of general medical devices, a self-declaration system is adopted.
2. Designated Controlled Medical Devices are to be certified by the third-party certification bodies based on Certification Criteria (discussed below) which are pre-authorized by the Minister of Health, Labour and Welfare (hereafter MHLW). Other Controlled Medical Devices are reviewed by the Pharmaceuticals and Medical Devices Agency (PMDA).
3. Specially Controlled Medical Devices are to be reviewed by PMDA and approved by the MHLW. They are reviewed based on separately specified approval criteria or Guidance Documents, which are authorized by the MHLW.

Where some devices comply with specified certification criteria and authorized by the MHLW they are to be reviewed and certificated by the third-party certification bodies as designated specially controlled medical devices.

PMDA reviewing applications for medical devices are as follows:

1. New medical devices: marketing applications for medical devices that have a clearly different structure, usage, indication, performance, etc., as compared to those that have already been approved for marketing.
2. Improved medical devices (with clinical data): marketing applications for medical devices that do not fall under "new medical devices" or "generic medical devices".
3. Improved medical devices (without approval criteria, without clinical data): marketing applications for medical devices that do not fall under "new medical devices" or "generic medical devices" (limited to devices for which no clinical data are required to be submitted).
4. Generic medical devices (without approval criteria, without clinical data): marketing applications for medical devices that are regarded as substantially equivalent to existing approved medical devices in terms of structure, usage, indications, performance, etc. (limited to devices for which no clinical data are required to be submitted).
5. Generic medical devices (with approval criteria, without clinical data): marketing applications for medical devices that are regarded as substantially equivalent to existing approved medical devices in terms of structure, usage, indications, performance, etc. (limited to devices for which no clinical data are required to be submitted.) and that comply with approval criteria (discussed below).

4.5 International Technical Standards

Standards play a significant role in the design, production, post-production and regulation of medical devices throughout their lifecycle. International standards offer important technical tools for conformity assessment, helping the evaluation that devices are safe and perform as intended.

Standards offer a means to streamline and harmonize regulatory processes around the world, especially as medical devices grow in complexity and as international markets expand. Standards can be particularly valuable as they reflect the state of the art and "*. . . generally reflect the best experience of industry, researchers, consumers and regulators worldwide, and cover common needs in a variety of countries. . .*" [13].

In general, the use of standards is voluntary, except in those particular cases where certain standards have been deemed mandatory by a regulatory authority.

Standards are created and published by national or international standards organizations or by regulatory authorities. As for medical devices, the most relevant bodies are listed below:

International Standards Development Organizations:

- IEC—International Electrotechnical Commission
- ISO—International Organization for Standardization

European Standards Development Organizations:

- CENELEC (European Committee for Electrotechnical Standardization) (https://www.cenelec.eu)
- CEN (European Committee for Standardization) (https://www.cen.eu)

US Standards Development Organizations:

- AAMI Association for the Advancement of Medical Instrumentation (http://www.aami.org)
- ANSI American National Standards Institute (https://www.ansi.org/)
- ASTM American Society for Testing and Materials (https://www.astm.org)

Japanese Standards Development Organization:

- JISC Japanese Industrial Standards Committee (https://www.jisc.go.jp)

For some standards, the development may be done by joint commissions (e.g. IEC and ISO).

Various terms are used to describe the characteristics of a standard. These are not necessarily mutually exclusive:

- basic safety standards (also known as horizontal standards)—standards indicating fundamental concepts, principles and requirements with regard to general safety aspects applicable to all kinds or a wide range of products and/or processes (e.g. standards concerning risk assessment and control of medical devices).
- group safety standards (also known as semi-horizontal standards)—standards indicating aspects applicable to families of similar products and/or processes referring as far as possible to basic safety standards (e.g. standards concerning sterile or electrically powered medical devices).
- product safety standards (also known as vertical standards)—standards indicating necessary safety aspects of specific products and/or processes, referring, as far as possible, to basic safety standards and group safety standards (e.g. standards for infusion pumps or for anaesthetic machines).

Standards covering different aspects of particular matter (e.g. safety of electrical medical device) or different types of device within a particular group (e.g. active implantable device) may have complex hierarchical structures (e.g. precedence) and interrelations. Standardized rules are used for the naming of standards belonging to the same series ("family").

An example of structure and naming adopted in IEC family of standard is depicted in Fig. 4.4.

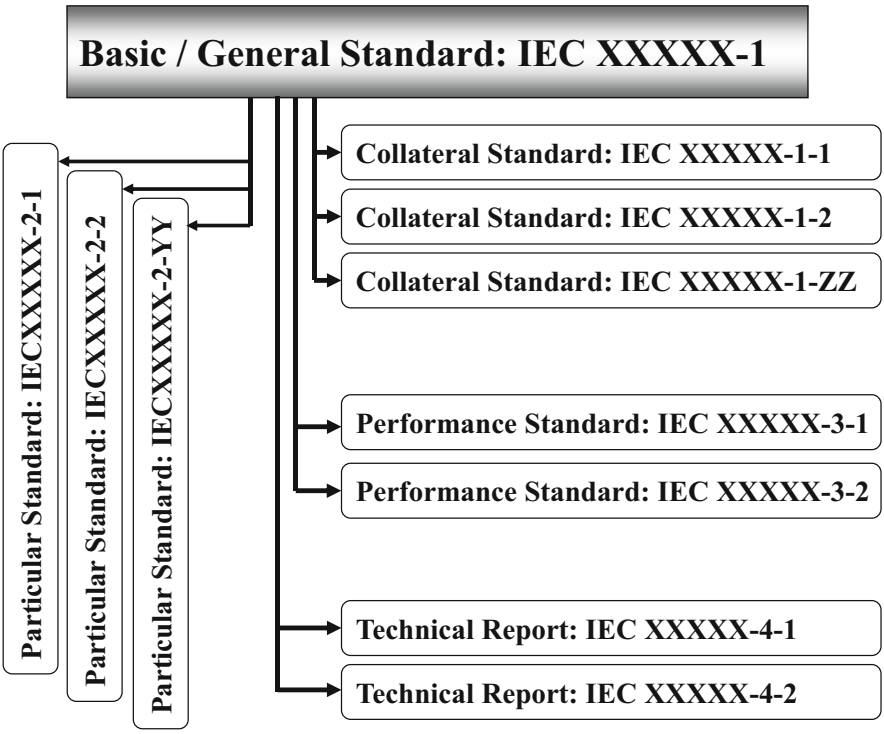

Fig. 4.4 General view of structure and naming of IEC standards

The most extensive family of medical device standard is the 60601 (Fig. 4.5), which addresses the safety and effectiveness of medical electrical equipment. The basic/general standard is formally known as IEC 60601-1—Medical electrical equipment - Part 1: General requirements for basic safety and essential performance. Compliance with this standard has become a de facto requirement for bringing new medical devices to market in many countries. The European (EN 60601-1) and Canadian (CSA 60601-1) versions of the standard are identical to the IEC standard.

There are also deviations from the standard that relate to country-specific requirements. Within IEC 60601-1, there are "collateral" standards that are denoted as IEC 60601-1-x; for example, IEC 60601-1-2 is the EMC collateral standard mentioned above. Other collateral standards include 60601-1-3, covering radiation protection for diagnostic X-ray systems, 60601-1-9 relating to environmental design, and 60601-1-11 recently introduced for home healthcare equipment. There are also many "particular" standards, denoted as IEC 60601-2-x that define specific requirements related to particular types of products, e.g. 60601-2-16 covers blood dialysis and filtration equipment.

The 60601 family covers several issues related to safety: electrical shock hazards and mean of protection; mechanical hazards (e.g. moving parts, pinching, crushing, over tilt, expelled parts, dropping, supports breaking); radiation hazards; ignition

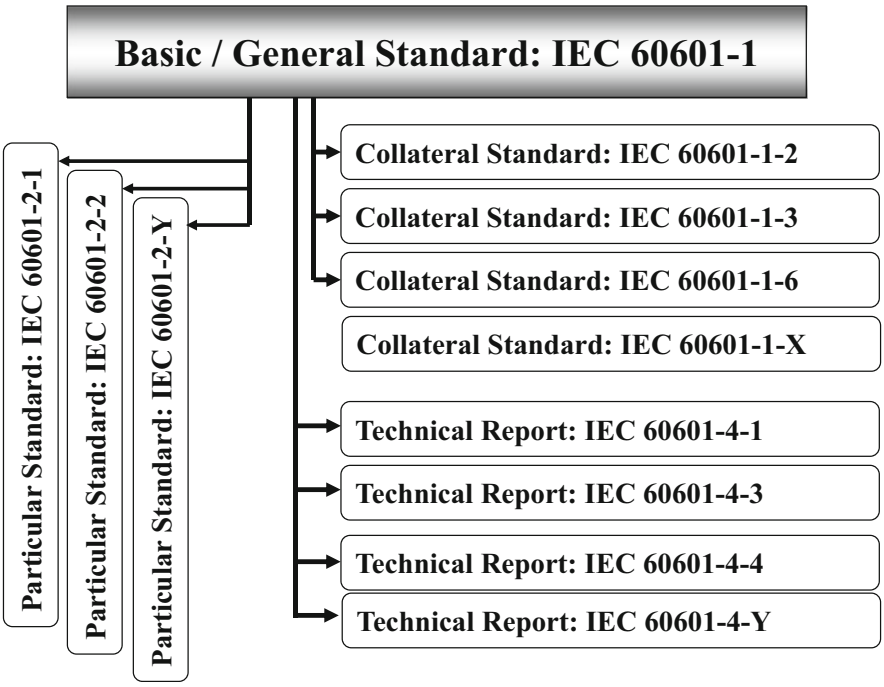

Fig. 4.5 Partial view of the 60601-1 family of standards

hazards of flammable anaesthetics; fire and other hazards; exposure to excessive temperatures, liquid spillage, pressure vessels, human errors and other such hazards.

Biological hazards (biocompatibility) are out of the scope of this standard, and are covered by the international standard family ISO 10993.

Sections 1 and 2 of IEC 60601-1 address the general requirements for tests (such as definitions and classification) and environmental conditions (including temperature, humidity, supply voltage and others). Section 9 identifies abnormal and fault conditions which must be evaluated. Section 10 addresses the general construction requirements for enclosure, components, and grounding (or earthing) that are not included in the other sections.

The up-to-date edition of this standard specifically calls out the Risk Management Process described in ISO 14971 that includes a risk management file where identifiable fault conditions are identified and assessed.

4.5.1 Harmonized Standards in Europe

In Europe, manufacturers working under the Medical Device Directives (MDD, AIMD or MDR) are given a legal "presumption of conformity" with essential

requirements if they apply harmonized standards as published in the Official Journal of the European Communities. Article 5 of MDD and AIMD state that "*member states must presume compliance with essential requirements if harmonized standards are applied*". In other words compliance with standards is voluntary, whereas essential requirements have the highest priority and must anyhow be fulfilled. In this context, standards are just one way to show compliance. If a manufacturer does not apply a harmonized standard, there is an obligation to document the solutions for fulfilling the essential requirements. The "presumption of conformity principle" is still present in MDR (Article 8).

4.5.2 Harmonized Standards in the USA

Whilst manufacturers are encouraged to use FDA-recognized consensus standards in their premarket submissions, conformance is voluntary. Demonstrating conformity with FDA-recognized standards facilitates the premarket review process. Standards that have been recognized by the FDA (either wholly or in part) are maintained and are searchable in the FDA's Recognized Consensus Standards database [14]. Standards for which a non-recognition determination has been made are listed in the Non-Recognized Standards database. A manufacturer may not declare conformity to a non-recognized standard.

Conclusion

The term "medical device" covers a very wide range of products, such as instruments, software and materials. Although the definitions of medical device may differ among national legislations, most of the definitions are based upon two principles: the medical purpose (i.e. the use for diagnosis, prevention, monitoring and treatment of disease) and the mechanism of actions (i.e. not based on pharmacological or metabolic or similar means). The classification of medical devices is a "risk-based" system based on the vulnerability of the human body taking account of the potential risks associated with the devices. Despite global efforts to harmonize regulation of medical devices via groups such as the Global Harmonization Task Force (GHTF), and the International Medical Device Regulators Forum there is a huge discrepancy among regulatory requirements all over the world.

In addition, technical standards offer a means to streamline and harmonize regulatory processes around the world, especially as medical devices grow in complexity and as international markets expand. Standards can be particularly valuable as they reflect the state of the art and reflect the best experience of industry, researchers, consumers and regulators worldwide.

Take Home Message

- The term *medical device* covers a very wide range of products, such as instruments, software and materials. Most of the definitions applied in the local regulations are based upon two principles: the medical purpose and the mechanism of action.
- The classification of medical devices is a "risk-based" system founded on the vulnerability of the human body and taking into account of the potential risks associated with the devices. The adopted criteria for this evaluation include parameters like duration of contact with the body, degree of invasiveness and local vs. systemic effect.
- In Europe, an important step is the introduction of the EU-MDR which includes, among others, new strict requirements as the identification of the responsible person for regulatory compliance, the implementation of the unique device identification (UDI) for better traceability and recall and the rigorous surveillance by Notified Bodies to reduce risks generated by unsafe devices.
- Technical standards offer a means to streamline and harmonize regulatory processes around the world, especially as medical devices grow in complexity and as international markets expand.

References

1. Global Harmonization Task Force (2012) Definition of the terms medical device and in vitro diagnostic (IVD) medical device. World Health Organization, Geneva. http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n071-2012-definition-of-terms-120516.pdf. Accessed Aug 2020
2. Global Harmonization Task Force (2012) Principles of medical device classification. World Health Organization, Geneva. http://www.imdrf.org/docs/ghtf/final/sg1/technical-docs/ghtf-sg1-n77-2012-principles-medical-devices-classification-121102.pdf. Accessed Aug 2020
3. Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices
4. Council Directive 93/42/EEC of 14 June 1993 concerning medical devices
5. Directive 2007/47/EC of the European Parliament and of the Council of 5 September 2007 amending Council Directive 90/385/EEC on the approximation of the laws of the Member States relating to active implantable medical devices, Council Directive 93/42/EEC concerning medical devices and Directive 98/8/EC concerning the placing of biocidal products on the market
6. Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
7. Manual of Borderline and Classification in the Community Regulatory Framework for Medical Devices. Version 1.22 (05-2019). https://ec.europa.eu/docsroom/documents/33704. Accessed August 2020
8. MEDICAL DEVICES: Guidance document—Classification of medical device—MEDDEV 2. 4/1 Rev. 9 June 2010

9. CFR—Code of Federal Regulations Title 21—Food and Drugs—Chapter I—subchapter h medical devices. https://ecfr.federalregister.gov. Accessed Aug 2020
10. Product Classification Database. Food and Drug Administration. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPCD/classification.cfm. Accessed Aug 2020
11. Government of Japan. Pharmaceutical Affairs Law (PAL). 1960 Act No. 145
12. Government of Japan. Pharmaceuticals and Medical Devices Act (PMD Act). 2013 Act No.84. [13] Essential Principles of Safety and Performance of Medical Devices and IVD Medical Devices. IMDRF Good Regulatory Review Practices Group. 31 Oct 2018. http://www.imdrf.org/docs/imdrf/final/technical/imdrf-tech-181031-grrp-essential-principles-n47.pdf. Accessed Aug 2020
13. International Electrotechnical Commission. Developing International Standards. http://www.iec.ch/about/activities/standards.htm?ref=home. Accessed Aug 2020
14. Recognized Consensus Standards Database. Food and Drug Administration. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfStandards/search.cfm. Accessed Aug 2020

Chapter 5
Lifecycle of Medical Devices

Federica Censi, Giovanni Calcagnini, and Eugenio Mattei

Abstract Medical devices are used on people to improve their health status or their quality of life. This unique characteristic calls for the strict monitoring of their overall lifecycle. For this reason, it is mandatory to ensure the strict compliance to standards and regulations: from the conception phase to the final use and final disposal of the obsolete devices. An additional important aspect is to ensure the post-marketing surveillance as an effective strategy to spot any potential flaws of a device and allowing for continuous improvements and reduction of potential risks. The correct use of medical devices, through clear and comprehensive instructions for use and adequate training is another important tool to ensure patients and operators safety.

The global nature of the medical devices market stresses the requirement to comply with international regulations, but also to the need for registering and licensing the device in the different countries where the manufacturer would like to sell.

This chapter considers all the above aspects and is completed with a case-study relevant to the development of a device for cardiac arrhythmia detection.

Introduction

The lifecycle of medical devices is similar to that of any technological product, in the sense that they begin their life in a manufacturing plant, then are sold to the end user and can be used up to the natural end of their lifecycle. However, medical devices have unique characteristics. Medical device companies are responsible for the safety and efficacy of their products throughout the lifecycle of the medical device, creating the need for rigorous pre-market testing and post-surveillance activities to monitor the technical and clinical performance of medical devices.

This chapter explains the phases of the lifecycle of medical devices, highlighting the peculiarities present in each phase compared to other products on the market.

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The development of a device for cardiac arrhythmia detection, for personal use, will be presented as a case-study.

5.1 Medical Devices Lifecycle: WHO Definition, Main Phases, and Stakeholders

The concept of a lifecycle for medical devices is adopted from the broader idea of a product lifecycle (PLC). Like all products, a medical device begins its life as an idea that has to be put into effect by an adequately managed manufacturing process, then sold to the end user and used until the natural end of its lifecycle. Making sure that product development meets all regulatory requirements from the very first stages to the end, is most important to guarantee the success of the device in the market and the safety for the users. Among the different definition of the PLC for a medical device, the one given by the WHO (World Health Organization) in the guide "MEDICAL DEVICE REGULATIONS - Global overview and guiding principles" is particularly suitable to understand how the regulatory system plays an important role during all the phases of the PLC, and that any of these phases can affect the safety and performance of the medical device. Specifically, the WHO guide recognizes seven major phases in the life span of a medical device (Fig. 5.1) [1]:

1. *Conception and development*
2. *Manufacturing*
3. *Packaging and labelling*
4. *Advertising*
5. *Sale*
6. *Use*
7. *Disposal*

Of course, before a medical device is sold it must have been tested and approved in medical trials. The WHO guide also points out the persons (stakeholders) who directly manage the different phases of medical devices: the manufacturer (who usually manages the first three phases of the medical device's life span), the vendor (e.g., importers, distributors, retailers, and manufacturers who sell medical equipment), and the user (professional in a healthcare facility, or patient) are the three main actors who are directly involved with the different phases of the medical device PLC. Besides them, the Public/Patient and the Government are also key interested parties. The public are the ultimate beneficiary of medical devices, and in the case of over-the-counter (home-use) devices, they are the user as well. The government has the responsibility of overseeing that medical devices sold in the country are safe and effective.

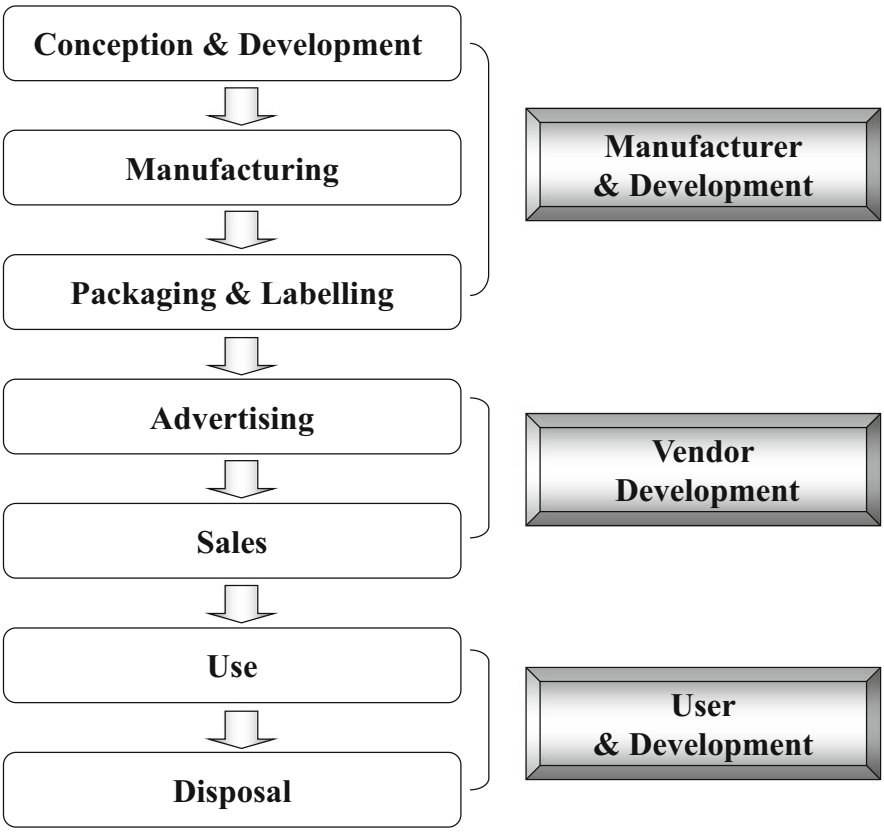

Fig. 5.1 The seven major phases in the life span of a medical device recognized by the World Health Organization

5.1.1 Phase 1: Conception and Development

The medical device (MD) conception is an essential element of the device's PLC, because it specifies both its functional safety and usability, therefore enables containment of error-prone processes.

In the conception phase, the medical device exists only as an idea. The first question the manufacturer has to ask is whether the intended product behind the idea will be a medical device. Generally speaking, a device intended to be used for medical purposes is a medical device (cf. definition of medical device on Chap. 4). Each medical device begins as an idea for solving a medical problem. These ideation processes generate abstract concepts needing refinement and development to become a practicable base for the production of a medical device that is effective, safe, and feasible to produce and to achieve regulatory compliance.

In this phase, the manufacturer begins an initial evaluation of possible development of a commercial product, which involves both economic and technical aspects. The manufacturer is expected to explore the funding strategies and the potential markets and distribution routes, taking in mind that medical device market has its own regulations and challenges. At this stage the analysis of the clinical needs associated to the device and the impact of potential competitors can help. If the product contains an innovation so that the device has never been produced before, the invention should be protected by patenting it. Also, if there aren't equivalent devices on the market a clinical trial for the product is needed, which increases the budget due to the high costs involved. If the result of this initial evaluation is that the device has a market position and is viable and financially feasible, it is worth developing a working device (prototype) that proves the idea.

At this point, it is important to define the product and its intended use and to establish basic claims for the device in terms of both safety and effectiveness. This can be done by collecting user needs and translating them into technical requirements for the final product. The listings of the technical requirements must take into account the peculiarity of medical devices which must also comply with specific requirements in terms of both safety and performance. Such requirements have an impact on the medical device design since they concern many aspects from electromagnetic compatibility to the IP (Internal Protection) grade.

Soundness of concept and adequacy of design, construction, and testing (including verification, validation, and clinical trials) require the scrutiny of scientific experts to ensure that design parameters and performance characteristics do not impose unwarranted risks. Among the expertise that must be considered from the very beginning of the MD conception, the regulatory aspects play a crucial role. MD regulation often implies strict and specific design rules (e.g., regarding electrical safety, electromagnetic immunity, user interface) that do not apply to common devices. Conception and design of the device not taking into account what is prescribed by MD regulation is one of the most common cause of failure, especially for those manufactures who, for the first time, approach the MD market. A poorly designed device will not make its way through regulatory compliance into the market. In the unlikely event that it does, the lack of an adequate design taking into account all the aspects required by the MD regulation can lead to the failure to safely perform as intended and will undermine conformity with essential requirements.

To this regard, another important issue is the classification of the medical device, which can be different from country to country, since several different international classification systems for medical devices are still in use in the world today (see Chap. 4). However, the classification of medical devices is generally based on their intended use, invasiveness, duration of use, and the risks and potential harms associated with their use. The term "medical device" refers both to highly sophisticated computerized medical equipment down to simple wooden tongue depressors. The more complex the device, the higher the risk of user error. The classification is key in the determination of the conformity assessment route (e.g., CE marking) that

will ensure that the device will meet the applicable regulatory/clinical/quality requirements in a specific country.

Once the basic claims have been defined and the medical device has been classified, the developer may start creating a strategy to comply with regulatory prescription and building a design file from prototypes to the final product on the market.

The development planning consists of the design process including iteration on product design, prototyping, design review, verification, validation, and design changes. The device begins to take shape and it is expected to undergo some trials for which acceptance criteria must be clearly determined. A design trace matrix is a good way to track the device claims, in terms of mode of testing to verify and validate and equipment needed. In the validation phase, medical device companies conduct clinical validation activities to verify that the device is safe and effective. Clinical validation may require clinical trials if there aren't equivalent devices on the market. In this case, a clinical trial plan must be developed, which will use product from the final design and which should take into account potential external approvals, such as from an Ethical Committee. Clinical plan could also be based on a bibliographic research on existing publications and state of the art relevant to other equivalent devices.

The design of a medical device aims to define and implement the necessary specifications (i.e., intended use and expected performances) and exclude all potential hazards related to the intended use through the risk assessment process and conformity with national and international safety requirements. In the risk management process, all the potential failures of what can go wrong due to bad design, poor process or bad manufacturing, user failures by foreseeable misuse must be analyzed, as well as all measures that could control the harms from these failures. The results of risk analysis may even cause a design change.

In defining the regulatory strategy, it is important to take in mind the regulatory requirements of the country/region where the device will be sold: the requirements in the USA differ to those in Europe and even if there is very strong overlap, the submissions process is different (see, e.g., Chap. 4).

However, to fulfil normative requirements worldwide, all the validation and verification tests of the product must be passed. The manufacturer must gather all the evidences of proper design development and device testing. It is thus crucial to know the regulatory requirements for the product, to understand the real reason of each test and not to take shortcuts. The technical documentation will be reviewed/audited by a competent authority (e.g., Notified Bodies in Europe) for completeness against their expectations.

Besides developing a device which fulfils all the technical requirements, the manufacturer is expected to be able to replicate it in production. Thus, medical device product design should be carried out with the manufacturing process in mind.

5.1.2 Phase 2: Manufacturing

For a device to be commercialized, the design outputs must be transferred to the production, putting in place the equipment and methods to make the product in larger quantities assuring quality and consistency. At this stage the design is expected to be "frozen" and the product should be in the form that it will assume when it is commercialized.

However, the manufacturing process must be designed from the early stages of device design, to achieve seamless transitioning from design to the manufacturing phase. The manufacturer should layout and describe in detail all of the medical device's assembly steps, taking into account practical manufacturing limitations, ease of components assembly, and cost-efficient processing. This helps identify critical issues and potential interruptions. The products and its components could be partially adapted to manufacturing constraints, mainly coming from mass production processes.

Mass manufacturing of the medical devices is challenging because products must be produced on time, within budget constraints, and with reproducible quality of manufacture. Continuous process improvement based on internal and external feedbacks can help in resolving any issues and produce a better product.

Extensive and rigorous rules regarding the conduct and management of manufacturing must be implemented and followed. Since different products are made in different ways, each company must develop its own standard operating procedures (SOPs) and validation plans. By this means it is possible to govern manufacturing equipment and processes, as well as activities such as those related to product packaging and distribution that might affect product quality. Given the importance of a medical device, the manufacturing process is controlled by the competent authorities worldwide. The approaches used vary from country to country, but usually manufacturing sites are audited and procedures are checked meticulously.

First of all, manufacturing processes should be validated to ensure that the products are consistently defect-free. Validation is intended to assure that the manufacturing process only releases products that conform to the specifications and will work exactly how they are intended to be used. Medical devices are too important for the patient's safety to allow that even a single device reaches the market with defects and fails to meet all specifications.

The validation should ensure that when the process operates correctly, it produces only products conforming to specifications. When all of the procedures and equipment used in the manufacturing process are tested, manufacturers can have the assurance that the production lines they build will yield exactly the desired device.

Another important issue concerns the changes to the manufacturing process after initial production is underway. This could happen for several reasons such as the availability of new or less expensive components, new or additional safety procedures needed, different storage methods, availability of more precise and accurate

inspection equipment or new suppliers or component vendors. Any of these changes must be documented and the new processes must be validated as explained before.

If a manufacturing process is outsourced, suppliers must guarantee consistent quality management and product conformity and safety. For this reason, they are usually subject to inspection and audit by the manufacturers and by the competent authorities (even without notice).

5.1.3 Phase 3: Packaging and Labelling

Medical device packaging is an important part of delivering the device to market safely and securely. It is important to consider each stakeholder in the package design process: not only the final user (healthcare professionals or patients), but also less obvious stakeholders that may include, for example, seal operators, labellers, sterilization technicians, warehouse personnel, and other factory employees. Properly packaged medical devices pose little risk to individuals handling them. This highlights the importance of well-designed packaging systems in delivering clean, sterile, and protected medical devices to the point of use. Shipping is one of the hazards a medical device and its packaging must survive. Subtle damage can result during transportation and handling unless the total packaging system is designed robustly and can withstand various stresses. Well-sealed packaging is essential for those medical devices that must be maintained sterile until its use. All these aspects must be adequately considered and addressed in the MD risk analysis and properly documented according to the Quality Management System (QMS) procedures.

Product labels on medical devices help to educate patients and care providers about how a device should be used, who should use the device, what risks the device could pose to the end user (patient or care provider), and how to operate the device safely. Broadly, a label can be considered as both the instructions for use and any other information that is related to identification, technical description, intended purpose, and proper use of the medical device. A label should not refer to shipping documents. Labels ensure that when a customer purchases a medical device, they have immediate access to the best information pertaining to the safe operation of the device. The specific requirements for labelling different MD will depend on the type and on the risk class of device. Manufacturers should determine the risk classification and intended use for their devices before developing detailed labelling requirements. All medical device labels are to include many information such as the name and address of the manufacturer, packer or distributor, along with adequate directions for use (see Sect. 5.2.3 for details). QMS requires that medical device companies establish and maintain a procedure to control labelling activities.

5.1.4 Phase 4: Advertising

Advertisement is important for every product, since a product won't sell itself, especially if no one knows about it.

In this context, social media posts can be used to catch the attention of patients while technical documentation can better explain to a physician the capabilities of the product.

The purchase of a medical device is much longer and complex from any other product, since the decision process requires a great deal of consideration and research. While planning the advertising strategy of the device, it is important to keep in mind that the purchaser's profile is very heterogeneous, it ranges from hospital administrators, ambulant physicians to even private persons with different medical literacy.

First it is important to make the audience aware of the device's existence, using press release, radio, TV, and online ads. Then the audience should understand that the device could help in the medical problem they are facing. Device guides, testimonials, both patients and doctors, and case studies that show positive outcomes for patients are powerful to convince the audience to purchase and to show competitive advantages of the product versus other options. Positive patient outcomes are an important part of a medical professional's consideration criteria. If the device is thought for medical professional, benefits for the patient should be explained in a not-simplified professional language.

Marketing materials including website may be reviewed by regulatory bodies, so any claims must be founded on scientific evidence and backed up in the regulatory submission. Since the medical device industry acts globally, the information leaflet must be offered in local languages.

5.1.5 Phase 5: Sale

Once a medical device receives approval to be marketed, the product enters the launch phase of its lifecycle.

First, since sometimes the regulatory compliance does not necessarily give the right to sell the product, it could be necessary to register or licensing the device and/or facility in the different countries where the manufacturer would like to sell.

Second, the product won't sell itself, and a solid network of sales and marketing professionals is needed.

The buyers of the device may be hospital systems, clinics, healthcare providers, physicians, patients, distributors, and in some countries even the government. Thus, the marketing plan must consider all these stakeholders.

The identification of the correct audience for the device is crucial, and the information needed to build target market are usually already present in the organization. Once a primary profile of the most important target person has been set, the

definition of a secondary audience which can influence the buying process may help, i.e., nurse, office administration, hospital manager.

The identification of the audiences, together with the knowledge of the needs they have, facilitate and define the messages able to speak to them.

For example, doctors can use an existing device to manage a certain medical condition, but it could cause serious complications. If these complications are such that some patients refuse treatment or some doctors are considered negligent, these are weaknesses for the target client to focus on. If the new device does not have these competitor flaws, it is important from a marketing perspective to inform potential buyers of the innovations that mitigate those risks and simplify their lives.

Distributors may help not only with the actual selling process but also with the marketing support, device assistance and organization of events, exhibition, conferences, and training courses. Training and support are essential for an efficient marketing and enable effective use of the product.

Also, distributors can be a valuable resource in terms of registration or licensing of medical devices in a specific country, providing proper services for communication and interaction with the competent authorities.

If a reimbursement strategy can be applied, it is important to understand the process in the different countries where the manufacturer would like to sell, taking into account that costs for procedures and products could be imposed by the governments. Thus, the device could be sold at different prices in different countries.

5.1.6 Phase 6: Use

A medical device must be used correctly. Correctly means to follow what it is specified in the *instruction for use* provided by the manufacturer. If a medical device is used following the instruction for use, the responsible for a failure of the device, which can anyway occur, is the manufacturer. If a medical device is not used following the instruction for use, the responsible for a failure of the device is likely to be the user.

Although this is true for every device, in the case of medical devices, a very different and particular aspect must be taken into account, namely that incorrect use can lead to not treating the patient or even to injuries or death of patient.

Many medical devices are based on important technological innovations and can be very complex in their use. The instructions for use are therefore extremely important and must minimize all associated risks, taking into account the profile of the user.

Users of medical devices can have a profound effect on their safety and effective performance. Unfamiliarity with a certain technology or operating procedure, and the use of products for clinical indications outside the scope of those specified in the labelling, can cause device failure even in the absence of any inherent design or manufacturing defects. Within the clinical engineering community, it is widely believed that user error underlies at least half of all medical device-related injuries

and deaths. The re-use of disposable devices contrary to the manufacturer's instructions, and without proper control or precautions for minimizing associated risks, can be dangerous. The lack of, or inappropriate, calibration and maintenance of medical devices can seriously jeopardize their safety and performance.

The risks derived from an improper use of the device become even more important when the device is intended to be used in an environment different from healthcare facilities, as the home environment. Because the home environment is fundamentally different and much more unpredictable than the clinical environment, home use of medical devices presents unique challenges, many of which have the potential to impact patient safety.

The maintenance and cleaning of the device must also be correctly and explicitly indicated in the user manual. The maintenance of an external defibrillator can foresee, for example, the need to turn it on every day and verify its correct functioning by means of the self-test to verify the presence of faults. Failure to carry out this procedure can put the patient's life at risk, if a breakdown occurs in the event that the defibrillator is needed.

These issues are often overlooked or underestimated. In order to minimize such potential risks, the manufacturer/distributor shall support continuously the user for the rest of the device life. EU and US regulations guarantee that the user shall be provided with comprehensive and easy-to-understand instruction for use, labels, warnings, precautions, and contraindications, but also with all the information needed for the proper maintenance of the device, to ensure the performance and the patient safety for the life of the device.

Instructions for use are to be designed not only to satisfy regulatory requirements but also to be clear and understandable for the users specified in the device's intended purpose. The language in which the instructions for use must be provided is determined by the states where the device is sold.

The user, in addition to having to strictly comply with the manufacturer's instructions, must also inform him if anomalies or abnormal behavior are found in the operation of the device. The presence of adverse events must also be managed at the level of the quality system, together with all the information coming from post-market surveillance, to understand if corrective actions are necessary to ensure patient safety (e.g., the recall of the device).

In fact, once a medical device has entered the market, it also enters the post-marketing phase of its lifecycle. At this stage it is necessary to conduct post-marketing surveillance actions to ensure that possible adverse events involving the medical device are promptly reported and to address any complaints. At this stage it is important to conduct follow-up clinical studies and possibly make improvements of the product.

5.1.7 Phase 7: Disposal

Disposal of certain types of devices should follow specific and stringent safety rules. For example, devices that are contaminated after use (e.g., syringes and tubing) or devices that contain toxic chemicals, can present hazards to people or the environment and must be disposed of properly. MD manufacturers must comply with a series of international standards that prevent the use of hazardous substances (e.g., the regulation for the Registration, Evaluation, Authorization and Restriction of Chemicals—REACH, and the directive for the Reduction of Hazardous Substances—RoHS), that can pose a risk when used or when disposed. As the final phase in the PLC, the disposal of a MD is a responsibility of the user. However, keeping in mind that the ideal conditions that will ensure the safety and performance of medical devices require shared responsibility by all stakeholders, it is important that the manufacturer provides within the instruction for use all the necessary information that must be followed to ensure safe disposal of obsolete medical devices.

5.2 Regulatory Requirements

5.2.1 Conception and Development: Harmonized/Consensus Standards

As already explained in Chap. 4 of this book, the regulatory aspects play a crucial role, and the regulatory design phase is as important as the device design phase. Thus, the two phases must start simultaneously and must be carried on in parallel. Many, if not all, of the choices in the design of a medical device cannot be made freely but they must respect specific requirements, from the selection of the microcontroller to the color of an indicator.

In the EU market, medical devices must comply with the essential requirements as set out in Annex I of the Medical Device Directive (MDD), which have become general safety and performance requirements in Annex I of the Medical Device Regulation (MDR).

Article 8 of the Medical Device Regulation (MDR) [2] with regard to the Use of Harmonized Standards specifies that "*Devices that are in conformity with the relevant harmonized standards, or the relevant parts of those standards, the references of which have been published in the Official Journal of the European Union, shall be presumed to be in conformity with the requirements of this Regulation covered by those standards or parts thereof.*"

Thus, which requirements of the regulation can be satisfied with any specific harmonized standard and which harmonized standards are expected to be applied are concerns to be addressed in the conception and development phase.

Although the application of harmonized standards is not compulsory, safety and performance can be demonstrated by applying other standards or methodologies only if the manufacturer demonstrate that the applied standard or methodology is equivalent to or better than the safety and performance demonstrated by the harmonized standards.

Harmonized standards are applied to product design to demonstrate a presumption of conformity with the General Safety and Performance Requirements (GSPRs) of Annex I in MDR.

As a guidance for the manufacturer in the completion of the medical device requirements checklist, harmonized standards often have an appendix (Annex Z) which provide a "map" from the clauses of the standard to the sections of the applicable regulation (e.g., MDR). Meeting these requirements in the standard gives the presumption of conformity to those parts of the regulation.

Some of the hundreds of harmonized standards can be considered applicable to the device under question, depending on the scope of the standard. Since such standards prescribe precise procedures to evaluate specific aspects and conditions, it is of utmost importance to identify applicable standards before starting the device design.

In Europe, harmonized standard can be searched for in databases of recognized standards maintained by Regulatory Authorities or webstores of standards organizations for the device type (e.g., ISO, IEC). A similar approach can be followed in the USA: standards that have been recognized by the FDA (either wholly or in part) are maintained and are searchable in the FDA's Recognized Consensus Standards Database [3] which is searchable in terms of product code. Standards for which a non-recognition determination has been made are listed in the Non-Recognized Standards Database.

Thus, during the phase of conception and development of a medical device, the manufacturer is expected to know the essential requirements indicated by EU regulation as well as the harmonized standards, if any, associated to the requirements. The most common requirements for an active medical device are:

- Electrical safety
- Electromagnetic compatibility
- Usability
- Biocompatibility
- Optional (if in the intended use): additional requirements for home use, alarm systems, emergency medical services environment

For example, IEC 60601-1-8 is a harmonized standard that applies to safety and performance of medical electrical equipment and provides specific requirements for alarm systems and alarm signals in medical electrical equipment and medical electrical systems. The scope of the standard concerns medical device when an alarm condition is present. If the alert signal is intended only to provide information to the user, it can be justified that the standard is not applicable. Otherwise, if the medical device provides an alarm condition, the standard applies and the alarms must follow specific requirements in terms of signal frequency and amplitude.

If a medical device represents an emerging technology, standards may not yet exist or be in a draft form. If a standard is in draft form, it may be worth asking to the Regulatory Authority whether and when the standard under development will be recognized.

It must be also considered that the standards evolve as they can be either amended or revised. There is usually a transition period established for manufacturers to identify the changes of the standards and to adapt to the amendments and changes introduced.

In Europe, after this transition period, presumption of conformity ceases. Thus, during the entire device lifecycle, manufacturers are expected to be aware of changes in the harmonized standards they have used to demonstrate the conformity to the essential requirements. A different approach is followed in the USA, where the conformity assessment shall not be repeated if a standard is updated.

The international standard ISO 14971:2019 [4] supports manufacturers providing a framework including risk analysis, risk evaluation, and risk control for risk management to be adopted not only in the design phase, but also in the following phase of development, manufacturing, as well as of monitoring the safety and performance of the device after sale.

Some degree of risk is obviously inherent to the use of any MD and this risk's acceptability level is often conditioned by the stakeholders' own perception of risk, cultural diversity, educational proficiency, and patients' profile. Therefore, understanding how users will interact with the MD within their environment is vital for good design. As such, during the design stage, the first thorough control of an MD is implemented as part of the Quality Management System (QMS) requirements. MD design control is currently regulated by the updated ISO 13485:2016 [5] and National and International guidelines such as FDA 21 CFR, Part 820 [6] and MDR 2017/745, which, while varying in scope, history, and phrasing, interrelate in regulating QM procedures used to corroborate intended performance and risk reduction for an MD.

5.2.2 Manufacturing: Good Manufacturing Practice and Quality Management System

Manufacturing process of medical devices must guarantee the release of only products that conform to the specifications defined by the manufacturer and will work exactly how they are intended to. From a regulatory point of view, such an approach is guaranteed if the manufacturer has a quality management system according to the international standard ISO 13485 [5].

A medical device quality management system (QMS) is a structured system of procedures and processes covering all aspects of design, manufacturing, supplier management, risk management, complaint handling, clinical data, storage,

distribution, product labelling, and more. Most medical devices will require some form of a QMS; the complexity of the QMS will vary based on the classification of the device

When applied to the manufacturing process, QMS requirements for MD impose strict quality assurance on every aspect of production. The result is a tightly controlled manufacturing system, commonly known as Good Manufacturing Practices (GMP), which reduces the likelihood of non-conforming products. This practice ensures consistency in the quality and provides the basis for greater reliability in device safety and performance. Elements of the quality system are periodically subject to audits, management review, and corrective or preventive actions that will maintain product quality. Continuous monitoring and corrective action requirements are interrelated to post-market surveillance previously described.

The key advantage regarding QMS is that they represent a preventive approach to assure medical device quality versus the previous reactive approach by inspection and rejection at the end of the manufacturing line. Prevention has been proven to be more efficient and cost-effective in controlling manufacturing processes and maintaining medical device quality.

It is important to note that since the majority of medical devices are in the medium- to low-risk classes, their compliance with regulations often depends upon the declarations of manufacturers. Thus the question of quality assurance naturally arises. This is why it is critical for manufacturers to conform with quality system standards and for this conformity to be subject to periodic audit by governmental or third-party agencies.

Quality system requirements can vary from country to county for their manufacturers, who are subject to periodic inspection by the government and/or accredited third-party agencies. The applicable standard is determined by the risk class of the device and depends upon the regulatory system of the country or region.

5.2.3 Packaging and Labelling: Information to Report and Symbols to Use

The packaging and labelling of medical devices are considered in the *General Safety and Performance Requirements* (GSPR, from MDR) in Europe and are also of considerable importance in the USA; in particular, they must be designed in detail and described in the technical documentation supporting the regulatory approval.

As for the other essential characteristics, also for the packaging and labelling of medical devices, international standards can be referred to. They define the information that must be given and how to report on it. In addition to what is reported in the "horizontal" standards, it is necessary to check whether specific indications are given in the "vertical" product standards.

There are also some FDA guidance documents that specify the labelling requirements for specific products or product categories [7, 8].

In the USA and in the EU, medical device labels must contain a Unique Device Identifier (UDI), a unique special barcode for each item which allows to adequately identify the product and the manufacturer. A UDI code aims at an unambiguous identification of a specific medical device. To ensure a globally standardized and harmonized system, the UDI code must be issued under the rules of a US FDA-accredited issuing agency or an EU-accredited assigning agency, which includes GS1.[1]

The symbols used in medical device labelling that convey information on the safe and effective use of medical devices are identified in the international standard ISO 15223 [9]. This standard is of great help to support the manufacturers in preparation of labelling and accompanying documents. The standard is applicable to symbols used in a broad spectrum of medical devices, which are marketed globally and therefore need to meet different regulatory requirements. Symbols may be used on the medical device itself, on its packaging or in the associated documentation.

5.2.4 Advertising: Local Laws and Truthful Statements

Advertisement has the potential to create expectations and powerfully influence the belief in a medical device's capabilities. In addition, misleading or fraudulent advertising of medical devices may increase sale. However, from the buyer's perspective, the purchase of an inappropriate medical device is a waste of money that may deprive the patient of more appropriate treatment and could lead to patient or user injury. In order to prevent misrepresentation of a medical device, its intended use and its performance, the medical device market is regulated by a series of national and international standards or laws that specifically address the advertisement of such items.

In general, advertising of medical devices is less regulated than advertising drugs.

Some European countries have no specific regulation but only general rules concerning the promotion of a medical device. Some other European countries as well as the USA have instead special laws, and even the involvement of health professionals in the advertisement of a medical device can be considered inappropriate or can be forbidden. Other legal issues to be considered before starting the promotion of a medical device refer to rules on data protection, consumer protection, product liability, safety and performance requirements and restrictions related to the age of the target group.

These must be always considered by the vendor when the MD is put into the market. In particular, every vendor's declaration on the medical device must be based on the clinical data that comes from:

[1] GS1 is a not-for-profit organization that develops and maintains global standards for business communication. The best known of these standards is the barcode, a symbol printed on products that can be scanned electronically. (Taken from Wikipedia—retrieved on May 18th, 2021)

- clinical investigation(s) of the device concerned
- clinical investigation(s) or other studies reported in the scientific literature, of a device for which equivalence to the device in question can be demonstrated
- reports published in the peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated
- clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up

In the promotion of the device, therefore, each characteristic mentioned must have a specific feedback from the clinical evaluation.

5.2.5 *Sales: Responsibility of Manufacturers, Distributors, and Importers*

The sale of medical devices is a critical stage that leads to the device being put into actual use. The requirements prescribed by the QMS regulations try to minimize the risk of exposing the public to low quality or ineffective devices. In the last years, and in particular with the new EU MDR, the regulatory requirements specific for vendors/distributors have become more explicitly formulated. Distributors have to verify that the medical devices they sell meet all the necessary requirements. In EU, for example, distributors must check whether the medical devices are CE-marked and have a valid declaration of conformity. Also, they must ensure that the *instructions for use* (IfU) and labels of the products are available in the official language of the countries in which the product is sold. In the case of imported medical devices, it must also be checked whether the importer fulfils his regulatory requirements. This means that the distributor assumes part of the responsibility for the conformity of the products. In case a distributor has reason to believe that a device is not in conformity with the requirements prescribed by the in-force regulation, he is not allowed to put the devices on the market, and is obliged to inform the authorities if he suspects that the product is falsified or poses a serious risk. In addition, the distributor should keep a register of complaints, of non-conforming devices and of recalls and withdrawals, which plays a key role in ensuring the traceability of the device. As a consequence of this joint responsibility, an intense cooperation between manufacturer and distributor is necessary, and the evidence of this cooperation has to be documented within the QMS of the manufacturer.

An important aspect which deserves particular attention is the regulation of the online market of medical devices. Similarly to drugs, some medical devices cannot be sold without prescription. Thus, in case the vendor makes these devices available online, a healthcare professional must be somehow involved. In addition, given the global nature of many e-commerce distributors, it is not easy to verify that the device sold online is compliant with all the national regulation in force in different countries.

As mentioned above, medical devices can be sold by the manufacturers themselves, by distributors, or by importers. Each of these actors has different obligations from a regulatory point of view that also vary from country to country. For example, a non-European manufacturer can sell in Europe but must have a legal representative in Europe. An importer of medical devices in the USA must register with the FDA.

5.2.6 *Use: Correct Information to the User and Post-market Surveillance*

Manufacturers are required to ensure that the instructions for use of their devices comply with regulatory requirements, both in Europe and in the USA. If the instructions for use do not comply with the regulatory provisions, the competent supervisory authorities can order a blocking of marketing or sales.

In fact, manufacturers can be held responsible not only for injuries resulting from the use of an unsafe or defective device, but also for injuries suffered by patients or users who have used the device improperly because the instructions for use were formulated in confusing, wrong, or incomplete way. This also applies to incorrect information in translated versions of the operating instructions. The responsible party is in any case the manufacturer, regardless of who the manufacturer has hired to translate the instructions for use.

Regulatory requirements for the instruction for use can be found in the MDR in Europe as well as in FDA guidance documents for the USA.

Once the device reaches the market and it is used by patients or healthcare professionals, the manufacturer must monitor the product on the market, assessing its positive and negative effects, implementing inspections, reporting adverse events, and addressing complaints.

This activity is defined as *post-market surveillance* and is regulated by precise rules and laws.

Indeed, competent medical device regulatory authorities are increasingly focusing on post-market surveillance, both in the United States and in the European market. On the other hand, post-marketing surveillance is an effective strategy to know in time potential defects in the design or implementation of a device, and to express the manufacturer's commitment to the end user, allowing for continuous improvements.

In Europe, regulations require manufacturers to implement a Post-Market Surveillance (PMS) plan as part of their technical documentation. The plan must produce PMS reports (PMSR, for class I medical devices) or periodic safety update reports (PSURs—Periodic Safety Update Report—for class IIa, IIb, and III medical devices).

These reports present results and conclusions of the data collected from the post-market surveillance plans, together with the rationale and description of any corrective and preventive actions (CAPA) taken.

Manufacturers should also report benefit/risk conclusions, key clinical follow-up results, sales volume, and characteristics of the estimated user population and frequency of use in the PSURs.

The PMS plan must proactively consider information regarding serious and non-serious incidents, side effects, trending reports, feedback or complaints provided by users, distributors or importers of the medical device, and information available on similar devices.

In the USA, the FDA has published a guidance document setting out recommendations for post-market surveillance [10]. The document is not binding, but it defines best practices for implementing the PMS process.

FDA may identify device issues that are appropriate for post-market surveillance at any point during the lifecycle of a device. Such issues may be identified through a variety of sources including analysis of adverse event reports, a recall or corrective action, to evaluate the safety and efficacy of devices that have undergone limited pre-market testing or to obtain more information on the performance of the device in real-world clinical practice.

In this case, the manufacturer is required to submit a PMS plan, which must include, among other things, a background, a description of the device, and directions for use.

The PMS plan must specify: the patient population to be analyzed (including inclusion and exclusion criteria for patients), the calculation of the statistically significant sample size, primary and secondary endpoints, a list of adverse events of expected complications, and an agreement to collect unexpected adverse events. The follow-up program should be detailed and described together with the duration and assessment procedures.

A final post-market surveillance report has to be presented to FDA, which will determine if the manufacturer has satisfied the PMS issue. Sometimes the results of the post-market surveillance raise new issues or questions, thus additional actions may be required, as for example changes to the labelling of the device, new post-market surveillance order to address new issues, or administrative actions.

In the next paragraph, a real example of the lifecycle of a medical device will be shown, from the initial idea to the marketing, which tells the path followed and the choices made in practice.

5.3 A Case-Study: Development of a Device for Cardiac Arrhythmia Detection, for Personal Use

5.3.1 Conception and Development: From the Idea to the First Prototype

The Clinical Need Unmet

The idea stemmed from the research activity of bioengineers, investigating, from an engineering point of view, cardiac arrhythmias, to improve understanding of the underlying mechanisms (Fig. 5.2).

In carrying out these research projects, in cooperation with clinicians and general practitioners (GP), they realized that one unresolved problem with cardiac arrhythmias was the timely detection. The pathology is in fact detectable only if it occurs during an electrocardiographic (ECG) examination (so-called occasional finding), which, due to the peculiar characteristics of this disease, remains a rather rare coincidence, being often asymptomatic and intermittent. Being asymptomatic, like a tumor in the earlier phase, it is unusual to undergo a medical examination for its specific assessment, so it happens to be affected when it is too late and, in most cases, when a concomitant and more serious pathology occurs. It also appears to be intermittent and leaves no marks, so very often it happens that it is not diagnosed during an occasional cardiology check-up. Its diagnosis is a real challenge. It is necessary to be in the right place at the right time. Or it would be necessary to undergo an ECG examination every day, to increase the probability of diagnosing it, but this solution was obviously not practicable, nor sustainable with the available technologies. In conclusion, an effective detection of cardiac arrhythmias was, at that time, a clinical unmet need for a very large portion of population.

Fig. 5.2 Device for arrhythmia detection for personal use

The Idea of the Device

The idea to meet the clinical need of a diagnosis turns out to be easily sustainable and practicable, by using the latest technological achievement in the field of electrical components and computational power. A device as small and light as a plaster, to be worn and used once or twice a day, on every day for a few minutes, allows to automatically detect the presence of this pathology. The device is attached to the patient by means of an adhesive electrode, similar, but not equal, to those used during an ECG examination. Once the ECG signal has been acquired, it is processed on-board and the results in term of diagnosis are provided by an immediate feedback directly to the user, like a thermometer for fever. The idea is simple but its realization required skills and in-depth studies. The major challenge is to "put" inside the device the knowledge of a cardiologist who can diagnose the disease. The algorithm that performs the diagnosis is the result of years of studies and has been patented. To move from the idea to the developing of a marketable device, a start-up was created and a fund-raising activity was carried out.

The Context

The alternatives that were on the market when the device was still just an idea were based on sending the cardiac signal data to a platform, where it was reported by medical personnel. These solutions have found limited interest and market development due to the lack of identification of the forms of reimbursement and financing. Further, the difficulties arose of overcoming the regulatory constraints of the medical sector by companies with consolidated positioning in different markets (ICT, internet applications). Another critical issue of these platforms is the fact that the technological skills necessary for their functioning are far greater than that possessed by the users of these solutions. People at risk, e.g., the elderly, in most cases still have major difficulties using a smartphone. The e-health solutions that involve the use of similar multimedia supports have in fact found little application all over the world. Finally, the need to have a team of medical specialists for reporting makes these solutions hardly sustainable for the national health systems worldwide. The solution implemented in the device does not require particular ICT infrastructures, nor data transmission or the presence of healthcare professionals. Intelligence is integrated, on-board, and patient feedback is immediate and simple, managed with an easily understandable indicator.

Thus, the device is highly innovative both from a technical point of view, given the innovative algorithm, and from the point of view of positioning on the market, since it is a self-measurement device for a specific pathology and does not require the intervention of a physician.

The Competitors

During the development of the device, other solutions have been developed and proposed to the market that allow the automatic home diagnosis of the pathology. Some solutions were based on the analysis of physiological signals other than ECG, a sort of a surrogate signal, whose characteristics may change when the disease occurs. The biggest flaw of these solutions derives from the analysis of a signal which is an ECG surrogate, and which leads to many misdiagnoses. Other existing solutions are represented by implantable technologies, which allow for continuous monitoring of the heart and therefore also for the diagnosis of disease. These devices represent an unsustainable solution in terms of cost and impact for the national health system (or other payers). In fact, the implantable devices must be inserted in the patient's body through a surgical intervention in the hospital. The price of such device ranges from 2500 to 3000 €, to which must be added the cost of the patient's hospitalization and the intervention. They are safe and reliable devices, but have been developed to diagnose other diseases. Finally, they are not self-measuring devices, because the data that the device records are sent daily to the reference clinical center for analysis, and therefore foresee a significant and practically unsustainable impact for the resources of the healthcare system.

More recently, other devices have been developed and marketed, very similar in terms of intended use, target population, non-invasiveness, and automatic diagnosis. The presence of equivalent devices has more *pros* than *cons* and it is always good news. Clinical studies of equivalent devices allowed to understand strengths and weaknesses of the proposed technology, leading often to improvements in terms of usability and accuracy. Furthermore, and not less important, clinical studies were precious resources in the clinical validation process necessary for regulatory aspects and they have been extensively cited and analyzed in the clinical evaluation report. Equivalent devices will serve as predicate devices in FDA pre-market clearance pathway, as a point of comparison to demonstrate substantial equivalence.

From a marketing point of view, little effort had to be made to lead the way, since potential users were already aware about the potential of innovation, having used equivalent devices.

The Requirements

The basic claims for the device in terms of both safety and effectiveness were:

- High quality ECG signal
- High accuracy algorithm
- On-board diagnosis using recommended guidelines
- Ease of use
- Reusable electrode
- Low overall weight
- Electrical safety

Table 5.1 Traceability matrix for the cardiac arrhythmia detection device

#	Requirement	Implementation	Verification criteria	PASS/ FAIL
1	High-quality ECG signal	State-of-the-art electronic components in the field of acquisition and processing of signals in the medical field and in abundance, according to the forecasts of the sector itself	Compliance with the IEC 60601-2-47:2012 Medical electrical equipment—Part 2-47: particular requirements for the basic safety and essential performance of ambulatory electrocardiographic systems	PASS
2	High-accuracy algorithm	Clinically validated algorithm using proper database	Compliance with the IEC 60601-2-47:2021 Medical electrical equipment—Part 2-47: Particular requirements for the basic safety and essential	PASS
3	Reusable electrode	Custom-made ECG reusable electrode	Minimum of 300 measurements with the same electrodes, without loss of ECG quality and diagnosis capability	PASS
4	Low overall size and weight	Use of small form factor surface mount electronic components; use of low consumption electronic integrated circuits, able to work with a single 3 V coin battery	Maximum size 6 × 4 × 1.5 cm; maximum weight 20 g	PASS
5	Ease of use	Stand-alone device with a simple interface based on a traffic light indicator, a single push button and a buzzer	Compliance with the standard IEC 60601-1-6 Medical electrical equipment—Part 1-6: General requirements for basic safety essential performance—Collateral standard: Usability	PASS
6	Electrical safety	3 V operating voltage; plastic case without any metallic parts; use of current-limiting resistors to limit current through the two patient electrodes	Compliance with the standard IEC 60601-1-Medical electrical equipment—Part 1: General requirements for basic safety and essential performance	PASS

These claims lead to the following technical requirements:

- State of the art electronic components in the field of acquisition and processing of signals in the medical field and available on large stock, according to the forecasts of the sector itself
- Surface-mount electronics for the acquisition of the EGC signal and for its subsequent conditioning and analysis
- Clinically validated algorithm using proper database
- Low consumption electronic integrated circuits
- Custom-made ECG reusable electrode

The requirements traceability matrix is reported in Table 5.1

The device shall comply with the regulatory frameworks for medical devices worldwide. Since the intended use is to make a diagnosis related to the cardiovascular system, the device has a moderate to high risk, which, for example, put it as a Class IIa device under MDR, and in class II in the USA, where it requires a 510k clearance.

As far as the regulatory requirements are concerned, the standards related to the electrical medical devices were taken into account, such as the 60601 family. In particular the standard about safety (IEC 60601-1), electromagnetic compatibility (IEC 60601-1-2 [11]), and home use (IEC 60601-1-11 [12]) were considered. Although there is no specific product standard for the device, the IEC 60601-2-47 [13] standard has been taken into consideration, since this standard is claimed in similar devices already on the market, and provides for tests both as regards to the electronics and as regards to any ECG signal analysis algorithms.

Also, since the device contains a firmware, the standard IEC 62304 for the software development has been accounted for.

Finally, the biocompatibility has been analyzed in order to pass the tests foreseen by the standard ISO 10993.

All these standards are recognized worldwide, so the compliance to them guarantees to overcome regulatory constraints in many countries around the world.

As a part of the validation, the clinical validation process has been of extreme importance. Since equivalent devices were already on the market, in terms of intended use and principle of functioning and usability, the clinical validation was based on the review of existing literature.

The Prototyping

The design process starts with a first prototype, involving component selection, development boards of the integrated chips and custom-made circuits using in-house resources for printed circuit board (PCB) and case prototyping. Since the prototyping phase, attention was paid to component cost and regulatory requirements. At this stage it was found to be cost and time effective to develop PCB using precision mill and cases using 3D printers. Up to 15 PCB prototypes have been designed and realized in order to optimize several aspects such as supply voltage, power consumption, means of electrical isolation, gain and resolution of the ECG front-end, and so on. The prototyping phase took about 3 years.

When prototyping was close to the final phase, the product was presented to a large company of electro-medical devices in order to have an industrial partner to move to the next phases of the project. The partner was selected among companies with a consolidated business in design, production, and distribution of medical devices. An agreement was signed for the development of the project. The agreement was based on the joint development of the device, leveraging the strengths of the two companies. This refers to strong market positioning worldwide, highly efficient/high quality manufacturing and leadership in personal health product innovation on the one hand, high scientific background in cardiovascular diseases, strong

commitment on research and innovation and high expertise in medical device regulatory field on the other.

This agreement made it possible to obtain the funds and the corporate structure necessary to reach the marketing stage. In particular, a strong industrial partner allowed for a more competitive and effective selection of suppliers and distributors.

5.3.2 *Manufacturing: Choice of Suppliers and Mass Production*

In the design of the device, the suppliers were identified for the following activities: PCB and component assembly, production of plastic case, production of packaging and labels, etc. In particular, four main suppliers were involved for the device: one for the PCB manufacturing and electronic components assembly, one for the device plastic case, one for the electrodes, and one for the final assembly and testing. These suppliers were chosen as a trade-off between cost and quality requirements (e.g., certification [6]) among those that already had a consolidated relationship with the industrial partner.

Once the project was frozen, it was possible to start developing the production procedures, indicating the methods and times in which each supplier had to operate. Particular attention must be paid to the Bill of Materials (BOM) and to the correct placement of the components on the PCB, to avoid high-rate failure during mass production. It was wise to stock up on the necessary components, since delivery times can be up to several weeks and production can be slowed down and delayed in the face of new orders.

In the production procedures, it was essential to indicate exactly all the actions that the workers will have to carry out, also with the help of photos and drawings.

A very important part is that relating to the final test, which was done in outsourcing. A specific testing bench has been first designed, then validated and adopted to verify all the most critical functionality of the device, before its release for sale. For the final test it was decided to produce log files in which the outcome of the test (positive or negative) was recorded, in order to be able to manage any traceability. Log files were regularly sent to the manufacturer for a double check. The activity needed to plan the mass production took nearly 1 year.

5.3.3 *Packaging and Labelling: A Compromise between Regulatory Restriction and Brand Message*

The packaging box was developed taking into account that, since the device was first sold in Europe, all the written information must be translated into 26 languages. Thus, it was chosen to privilege images that explain the use and content, describing

in words only the essential information, such as explanations of the indicators used in the device. The stylistic aspects were instead developed and deepened in order to recall the brand message.

The box has been designed in such a way that it can contain the device without damaging it, taking up as little space as possible. In addition, the volume occupied by the user manual, also necessarily translated into 26 languages, was considered.

Since the device is very small, the label on the device has been kept as synthetic as possible, reporting only the mandatory information according to the respected international standards.

5.3.4 Advertising: The Target is the Patient

The business idea, developed from a specific clinical problem and healthcare cost containment, is based on the intention of making the patient participate in the model of care. In fact, only the patient can carry out self-measurements on a daily basis, exactly as holds true so far for diseases such as diabetes.

The device is available for all patients (in particular for those at risk) in pharmacies (or para-pharmacies or stores for healthcare products) as well as online. Given the low cost of the device and the advantages in terms of savings for the healthcare services, forms of purchase incentives could also be considered, promoting the conscious participation of the entire population of an age judged to be at risk.

Customers are therefore the patients themselves who, to avoid serious consequences related to the disease, would be encouraged by physicians to purchase the product.

5.3.5 Sale: Distribution Network and Personnel Training

The marketing was entrusted to the network of agents, distributors, and importers of the industrial partner.

As the company was active in a medical field other than cardiology, it was necessary to expand the skills and knowledge of sales force.

It was very important to make the marketing personnel understand the strengths of the product compared to the competition, such as greater accuracy, the possibility of use with and without an "app," and the quality of the acquired signal. This was possible thanks to an intense training activity of company employees.

Furthermore, the direct sales channel in the pharmacy was an important challenge because it was outside the marketing activities carried out up to that moment.

Post-market surveillance is based on the procedures already set for other devices of the industrial partner.

5.3.6 *Use: Attention to Possible Misuses and Customers Reviews*

To avoid dangerous misuses of the device whose intended use is the exclusive diagnosis of a specific cardiac arrhythmia, many warning and caution messages were given in the user manual. They alert that other diseases that require emergency intervention or that are outside the intended use must be diagnosed and managed in other ways.

Another important issue concerning the use is the right positioning of the device on the body, so explanatory drawings were added to the manual to clearly outline the required placement.

The product will be used directly by patients, therefore in the analysis of the usability of the product, reviews available through social media (websites of online sales channels or of the industrial partner) will also be collected and evaluated.

Conclusion

Even though the lifecycle of medical devices follows that of other products, the peculiarities in terms of rigorous testing to be carried out, third-party controls and in general the guarantee of safety and effectiveness both before and after the sale, are evident. It is therefore of utmost importance to know all these aspects when deciding to develop a new medical device, so that it can be put to market ensuring the safety of users and improving the health of patients.

Take Home Message

- Being used on patients, medical devices are a special class of products and for this reason they must obey to a specific set of standards and regulations over their overall lifecycle. This compliance must be ensured by the different involved stakeholders, from the inventor to the final user.
- One important aspect is to ensure the post-marketing surveillance as an effective strategy to spot any potential flaws of a device and allowing for continuous improvements and reduction of potential risks.
- To reduce the risk for patients and operators, the correct use of medical devices must be highlighted. This brings special attention to the need of clear and comprehensive instruction for use and to the importance to ensure adequate training for professional or lay operators.
- The global nature of the medical devices market stresses the requirement to comply with international regulations, but also to the need register or licensing the device in the different countries where the manufacturer would like to sell.

References

1. https://www.who.int/medical_devices/publications/en/MD_Regulations.pdf. Accessed June 2021
2. Medical Devices Regulation (MDR) n. 2017/745
3. FDA Recognized Consensus Standards. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfstandards/search.cfm. Accessed 9 Mar 2021
4. ISO 14971 Medical devices—application of risk management to medical devices
5. ISO 13485: 2016 "Medical devices—quality management systems—requirements for regulatory purposes"
6. Code of Federal Regulation—Title 21—Part 820: quality system regulation. https://ecfr.federalregister.gov/current/title-21/chapter-I/subchapter-H/part-820. Accessed 9 Mar 2021
7. FDA 89-4203 Labeling—regulatory requirements for medical devices. https://www.fda.gov/media/74034/download. Accessed 9 Mar 2021
8. FDA Guidance on medical device patient labeling—final guidance for industry and FDA staff. https://www.fda.gov/media/71030/download
9. ISO 15223-1 Medical devices—symbols to be used with medical device labels, labelling and information to be supplied—part 1: general requirements
10. Code of Federal Regulation—Title 21—Part 822: postmarket surveillance. https://ecfr.federalregister.gov/current/title-21/chapter-I/subchapter-H/part-822. Accessed 9 Mar 2021
11. IEC 60601-1-2 Medical electrical equipment—part 1-2: general requirements for basic safety and essential performance – collateral standard: electromagnetic compatibility—requirements and tests
12. IEC 60601-1-11 Medical electrical equipment. General requirements for basic safety and essential performance—collateral standard: requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment
13. IEC 60601-2-47 Medical electrical equipment—Part 2-47: particular requirements for the basic safety and essential performance of ambulatory electrocardiographic systems

Part III
Engineering and Operations

Chapter 6
The Medical Devices in Healthcare Provider Organisations

Carlo Boccato

Abstract Medical devices impact the daily practice of healthcare provider organisations. Elements that contribute to the quality of the healthcare treatment and how they are organised will be discussed in this chapter.

Medical devices in their different declinations and definitions must be considered in respect to their overall life cycle to achieve the best results.

A healthcare provided organisation is a complex system characterised by many multifaceted and non-linear connections among the different components and actors. The adoption of complex medical devices introduces additional factors that increases this complexity. System thinking and a holistic approach are required for the successful management of the activities and to ensure safety and quality of care.

The case of haemodialysis treatment is taken as a paradigm for the application of a complex medical device system for the treatment of a chronic disease, analysing the impacts of the technology on the infrastructure and government of the healthcare provider.

Introduction

Elements that contribute to the quality of the healthcare treatment and their application and organisation need to be considered. In the following a comprehensive picture will be given about the introduction and operation of the medical devices of different complexity in Healthcare Provider Organisations (HPOs). The term HPO identifies every organisations devoted to the diagnosis and treatment of illness or making rehabilitation, considering both in- and outpatients. Most of the following considerations are valid both if the healing actions are conducted inside the organisation itself and when the medical device is used at patient's home under the supervision and responsibility of the HPO.

The starting point is the analysis of the elements that contribute to the quality of the service given to the patients and community and the impact that the application of medical devices has on these elements.

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To ensure the best effectiveness and efficiency, the decision maker should carefully consider all the aspects concerning the requirements and implications for the operation of the medical device along its complete life cycle.

An HPO can be described as a complex system characterised by many multifaceted and non-linear connections among the different components and actors. The healthcare system includes actors ranging from representatives of manufacturers and insurance companies as well as policymakers, to healthcare professionals and patients. The adoption of medical devices, besides the improvement of the patient's outcome, may introduce additional factors escalating this complexity. A holistic approach and a system thinking orientation are required for the successful management of the HPO and to ensure safety, quality of care and risk mitigation.

The case of dialysis treatment will be analysed as a possible paradigm for the application of complex medical devices to the treatment of a chronic disease.

6.1 Setting the Issue

In the following pages we will make reference to the concept of Healthcare Provider Organisation (HPO) as any organisation taking care of patients and aiming at the improvement of their health and quality of life.

This may span from a small single-speciality centre treating a single pathology to a large multi-speciality hospital. The successful operation of the HPO requires to focus on a variety of factors such as the quality of delivered care, the reduction or control of the risks for patients and caregivers and the efficient use of the resources.

An HPO, as most human organisations, can be described as a complex adaptive system (CAS).[1] To successfully manage an HPO many aspects and agents, usually interacting through non-linear relations should be considered. The introduction of a medical device or any complex technology generates different technical and administrative reactions and needs that must be governed [1].

The extensive use of medical devices has an impact on the design and government of the HPO. This is valid both if the device is operated inside the organisation and when it is used at the patient's home under the remote supervision and responsibility of the HPO. In this case, the institution's management should ensure that the patients and caregivers receive the adequate information and training (as applicable) and that the environmental conditions for the successful and safe operation of the device are met, e.g. granting hygiene and compliance to electric safety standards.

To analyse the topic, it is important to clearly define what it is intended with the term *healthcare technology* and what are the target of the HPO in terms of delivered performance and quality.

[1] CAS, a system such as a business or other organization that consists of many connected parts which should change as conditions change in order to succeed (from: Cambridge Business English Dictionary © Cambridge University Press).

6.1.1 Healthcare Technology and Medical Devices

The term *healthcare technology*, as emphasised in the following definition, may refer to a set of very different tools and methods including the medical devices themselves, pharmaceutical products, and vaccines. Although the latter are outside the scope of this book, they might be used in association with a medical device.

Health technology has been defined by WHO [2] as the "*application of* ***organized knowledge and skills*** *in the form of* ***devices****, medicines, vaccines,* ***procedures*** *and* ***systems developed to solve a health problem and improve quality of life****. It is used interchangeably with healthcare technology*" (terms emphasised by the author).

This definition stresses some very important elements. The objective to solve or alleviate health problems or to improve the Quality of Life (QoL) is achieved with:

- Use of devices
- Organised knowledge and skills
- Procedures and systems

It is underlined that the successful application of technologies in healthcare requires the background of a corpus of organised knowledge, skills and procedures.

The given definition of health technology makes reference to the large class of *medical devices*. For these, the most widely recognised definition is:

Medical device is any "*article, instrument, apparatus or machine that is used in the prevention, diagnosis or treatment of illness or disease, or for detecting, measuring, restoring, correcting or modifying the structure or function of the body for some health purpose. Typically, the purpose of a medical device is not achieved by pharmacological, immunological or metabolic means*" [2].[2]

As it can be inferred by this definition, the term medical device identifies a very wide category of products: from a simple wooden tongue depressor, to a Personal Protective Equipment (PPE), to a dialysis filter, up to the most complex magnetic resonance system.

It is also worth to add a further categorisation that can help to underline the difference between "simple" and "complex" medical devices that may involve a very different technical and managerial approach by the HPO.

For this reason, it is useful to add the definition of medical equipment as: "*Medical devices* ***requiring calibration, maintenance, repair, user training, and decommissioning*** *– activities usually managed by clinical engineers. Medical equipment is used for the specific purposes of diagnosis and treatment of disease or rehabilitation following disease or injury; it* ***can be used either alone or in combination with any accessory, consumable, or other piece of medical equipment****.*

[2] This definition is proposed by WHO, but is substantially in line with European Medical Devices Regulation (MDR) and other standards and normative references. Refer to Chap. 4 of this book for a further clarification of the topic.

Medical equipment excludes implantable, disposable or single-use medical devices" (terms emphasised by the author) [2].

The concept of medical equipment, even if not considered in these terms within standards like the European Medical Devices Regulation (EU-MDR), is helpful to emphasise the specificity of the more complex medical devices. They require calibration, maintenance, repair, commissioning/decommissioning and can be used in combination with other medical devices, like consumables.[3]

The words highlighted in this definition identify the main competence and responsibilities of managers and operators in the healthcare institution for the operation of complex medical devices over their full life cycle (see also Chap. 5).

The case of the artificial kidney or haemodialysis will be presented in Sect. 6.4 as a possible paradigm of the use of medical devices of different complexity for the treatment of a chronic disease.

The treatment is based on the use of a medical equipment that must be used in combination with consumable medical devices, like dialysis filters, tubing and needles.

6.1.2 The Quality in HPO

In recent years, great attention has been paid to the evaluation and possible improvement of the quality of the services delivered to patients by hospitals and other healthcare provider organisations. This, together with the cost reduction, is presently considered among the most important issues in healthcare management for the improvement of the value of care (see Chap. 10).

The use of medical devices and equipment has a strong impact on the performance and organisation of the HPO and is of course influencing the quality of the delivered treatment. For this reason and for the sake of our discussion, it is useful to make reference to a model describing the quality in healthcare. Many different approaches have been used to assess the quality of care delivered by a HPO, but the most commonly credited ones are the models developed by A. Donabedian and the one proposed by Lohr and Schroeder [3].

Despite already developed in 1966, the Donabedian's paradigm is still a widely accepted model for healthcare quality [3] and will be adopted to support the considerations in the following pages.

This model shows that the quality is obtained by the management of different activities and is constructed by the adequate contextual conditions [3].

This paradigm is based on three components, as summarised in Fig. 6.1.

[3] For the sake of brevity, the terms *device* will be also used when referring to *equipment* or *complex medical device*. The reader should anyway keep in mind the possible implications due to the difference between the two elements.

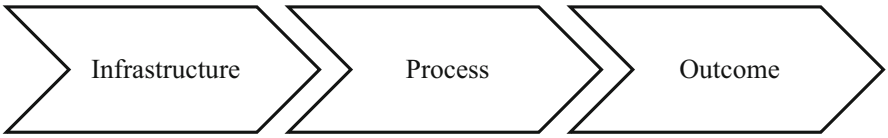

Fig. 6.1 The elements of the Donabedian's model for HPO quality. (Adapted from [4])

By ***structure*** the model refers to the factors related to the internal organisation and management system of the HPO. This includes the human, material and financial resources as well as the managerial actions to take care of these elements. In this text we will refer to this setting as "**infrastructure**" to emphasise the important contribution of the material resources (see also Fig. 6.2).

The second component in Fig. 6.1 concerns the ***process*** put in place to achieve the required results. This includes the technical competences in a broader sense, e.g. including both medical and engineering know-how, and the cooperation among the operators. Another key aspect is the implementation of the procedures aiming at the control and possible reduction of cost and risks connected with the treatment.

Results or ***outcome*** refer to the patient's health status, relief of symptoms, and improved functionality.

The term *outcome* includes the evaluation whether the goals of care have been accomplished, but includes also the evaluation of the final patient's health status, the cost of care and—not least—the patient's satisfaction and the sustainability of the achieved health status.

Even if not always considered in these terms and by the Donabedian's model, the results should include the creation of value for all the involved stakeholders. This includes the benefits for patients and community, the reduction of the cost for the payor for the treatment and the generation of appropriate profit for the HPO owner itself (see also Chap. 1).

It is also useful to split the outcomes into intermediate (like operating site infection rate) and final (i.e. the final effect of the provision of care, like health status, disability level or death) [4].

It is important to note that any healthcare action may have an impact not only on the patients itself, but also on patient's relatives and the whole community.

The contribution of patient's relatives is generally underestimated. Moreover, it can be expected that this involvement will not be available in the near future due to the new reality of the family and community organisation. This would lead to higher need for healthcare professionals and cause higher healthcare financial burden.

The health outcome involves the assessment of a set of specific indicators. These are based on patient's clinical status or on the measurement of the treatment performance (see Chap. 10). Both can, in many cases, directly be assessed by the medical equipment itself through the use of dedicated sensors and computation algorithms (see case report on haemodialysis).

In the following the analysis will be focused on the infrastructure and on the processes as they are influenced by the introduction of medical devices and equipment.

6.2 The Role of the Infrastructure

Many authors underline the importance of the infrastructure for the delivery of good healthcare services. The WHO includes the infrastructure improvement among the elements to overcome the weaknesses of many healthcare systems [1].

We define as *facility infrastructure* the set of all the components which allows an HPO to deliver the required services. Figure 6.2 gives a synthetic overview of the main elements. All these are strongly influenced by the introduction of the medical devices. In addition, due to the complexity of the HPO, any action affecting one of the components may have a strong impact on all other elements.

Making reference to the diagram in Fig. 6.2, it is possible to group the main factors in four main areas.

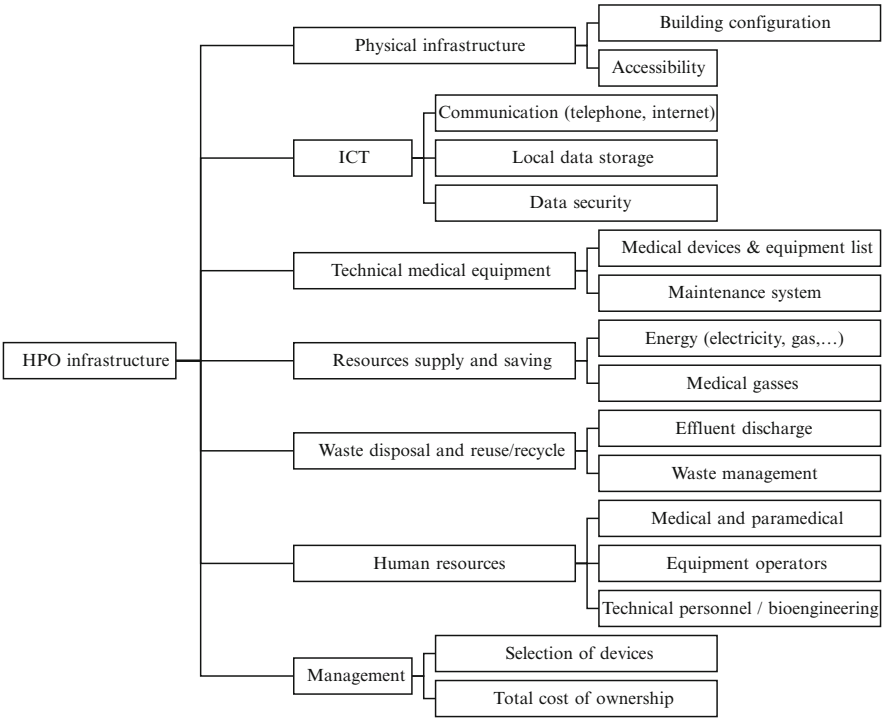

Fig. 6.2 The main components of an HPO infrastructure. *ICT* Information and Communication Technology. (Modified, reduced and adapted from [5])

1. **Physical and technological components**.

   The presence of medical equipment requires to pay attention to specific needs like:

   - Accommodation, that may require a special environment in terms of areas and possible specific local adaptations, e.g. magnetic field shield for the location where a magnetic resonance imaging (MRI) system is installed.
   - Easy access for patients, especially in areas for chronic treatment or diagnostic operations and a smooth workflow for personnel and material delivery, e.g. for consumables.
   - Information and communication technology resources, that are of special importance when data concerning diagnostic imaging must be collected, stored and distributed. Data security is also an important issue, as discussed in Chap. 7.
   - Availability of state-of-the-art and adequately maintained devices and equipment.

2. **Use of resources**.

   The operation of medical devices and equipment may imply a large use of material resources, including e.g. supply of electric energy over dedicated lines, medical gas and purified water. In many cases it must also be paid attention to the effluent fluids that may need specific treatment due to the possible presence of contaminated or toxic substances, like hazardous wastes, disinfecting agents or radioactive isotopes. In most countries, the limit levels of these toxic substances are stated by law.

3. **Human resources**.

   The healthcare institution has been traditionally seen in the past as a *non-technical* environment [7]. The application of (complex) medical devices opens an important set of considerations about the presence of in-house competences as well as the allocation of technical responsibilities. Apart from the obvious need to have well-trained medical operators in larger facilities, where many different pieces of equipment are in operation, the presence of technicians and bioengineers is necessary. These professionals can take care of all devices along their full life cycle: from procurement, operation and maintenance to decommissioning

4. **Management and governance capability**.

   Concerning the medical devices, the HPO management should be also involved in the selection of the devices and in the estimation and management of their total cost of ownership (TCO).

   The estimation and control of TCO is a very important management tool. It is defined as the financial estimation of all direct and indirect costs connected with the ownership and utilisation of a device/equipment or technology. Apart from the pure purchasing cost, it includes all the other costs related to procurement and storage of consumables, equipment maintenance, disposal of obsolete devices and training of personnel. The TCO also gives reason for the hidden costs that, on top of the purchasing price, may arrive up to 85% of the total cost during the overall device's life cycle.

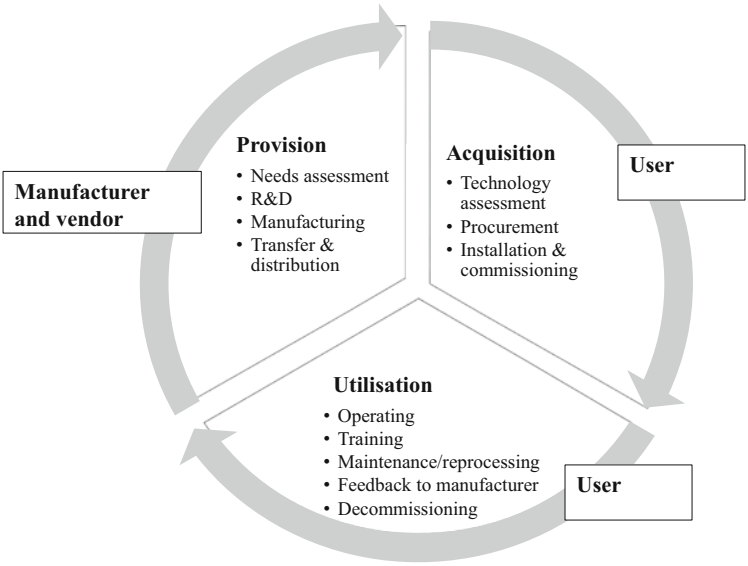

Fig. 6.3 The basic life cycle of a medical device and the actions to be undertaken by the main actors, such as provision, acquisition and utilisation. *R&D* Research and Development. (Adapted from [6])

The diagram in Fig. 6.3 shows the main activities to be undertaken by the responsible persons in HPO during the overall life cycle of the device or equipment. Many of these activities imply their strict relationship with the manufacturer/vendor.

As it can be seen from the above chart, the user's role does also include the feedback to the manufacturer/vendor to ensure the timely and continuous evaluation of the efficacy, performance and safety of the devices. This can be achieved by the strict adherence to the *post-market surveillance* program. A more detailed and comprehensive view of the medical device life cycle can be found in Chap. 5.

6.2.1 Acquisition

The acquisition procedure is based on the following steps:

- Assessment of the technology, to ensure it answers to care requirements and whether it is in line with the expectations and culture of the community to be served[4] [7, 8]

[4]This aspect is of special importance to guarantee that the community is willing to accept the medical acts involved with the technology and is available to pay for the delivered service. The acceptance of a medical practice is strongly related to the culture of the community and to the medical literacy of the involved stakeholders.

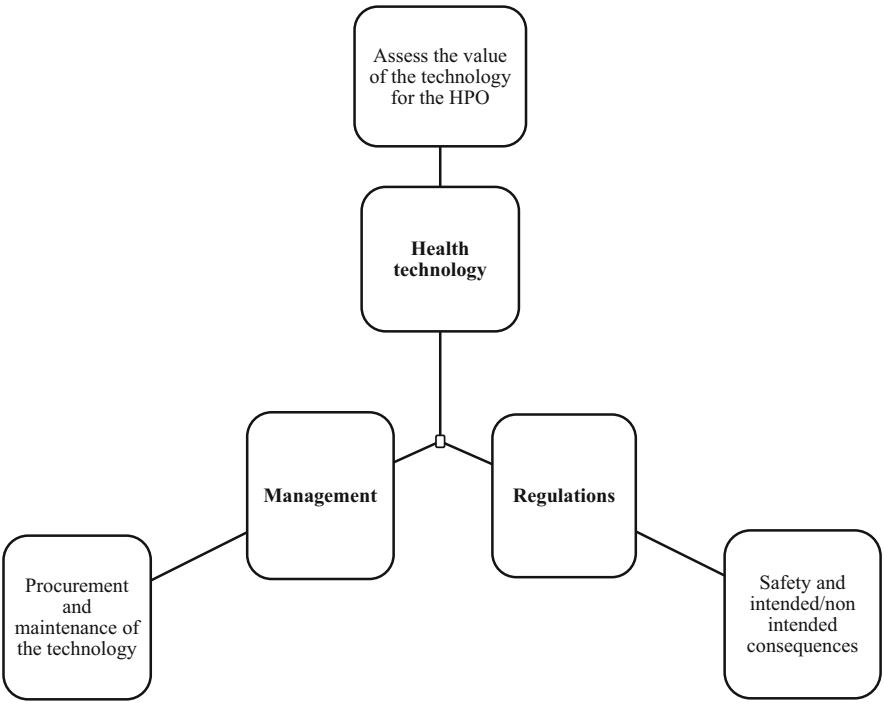

Fig. 6.4 The main aspects to be considered when selecting a medical device (equipment)

- Evaluation and planning of the service to be delivered to the community
- Placement into operation (it includes the availability of the required structural provisions as well as the requirements in terms of personnel and skills)
- Commissioning activity for complex equipment

The procurement activity requires the harmonisation among technical, regulatory and managerial competences as illustrated in Fig. 6.4.

After the assessment of the technology the decision maker should verify that the introduced medical equipment, and its application in the considered environment, is in full compliance with the applicable standards and regulations. This means that it is not only needed to have an equipment according to the required standards and directives, but also to ensure that the needed consumables, the environment and the resources are according to the applicable standards. A possible example is the requirement to have dialysis water in compliance with the best practice, international standards (e.g. ISO 23500-1-19) [9] and legal regulations.

This regulatory aspect also includes the required activities to ensure the safety levels and the risk control.

The safe and effective use of the technology entails the adequate management attention to all the above aspects. Considering the MD life cycle as proposed by the WHO [6] it is important to observe the role the final user has on the safe application

and performance of the medical devices, through the active participation to the post-marketing surveillance activity (i.e. feedback to the supplier/manufacturer as indicated in Fig. 6.3).

6.2.2 *Utilisation*

The user must always consider that each medical device has been designed for a specific **intended use**,[5] to work within well-defined conditions and operated accordingly by trained personnel.

The responsibility of the MD user begins when open the packaging, e.g. related to sterility and absence of pyrogens.

Besides the adequate operational environment and the training of the operators, it is mandatory to ensure the following conditions:

- Clear allocation and documentation of responsibility within the HPO, especially when concerned with complex equipment
- Ensure the maintenance by authorised personnel, that must be regularly trained and certified by the manufacturer or by its representative
- Provide the correct decommissioning of worn-out pieces of equipment and/or disposal of non-reusable items or disinfecting/reconditioning of the parts intended for reuse

For single-use devices, it is important to set up the suitable disposal system. Many of these devices, like needles, syringes or other parts that might have been in contact with body fluids, may be contaminated. Contamination may be due to pathological proteins or microorganisms and their disposal must ensure the safety of patients and operators that may come in contact with them and avoid the pollution of the environment.

In addition, the management should carefully consider the overall cost generated by the ownership and operation of the medical equipment. The *Total Cost of Ownership* (*TCO*) is here a useful concept and is one of the key points in the equipment selection process.

An additional important aspect is relevant to the management of the medical equipment. This is vital to ensure that the device is correctly operated and maintained, but also helps the allocation of the HPO's resources in the optimal way.

A single source database about all the medical equipment available in the HPO should be accessible by key persons and contain the following indications:

- Comprehensive device/equipment information (including technical specification)[6]

[5] A device designed for a defined intended use cannot be applied for alternative (not approved) application.

[6] Reference to the UDI (Unique Device Identifier) as defined by Article 27 of the 2017/745 and Article 24 of Regulation 746/2017 [11].

- Required operator's training and training status
- Location of the MD within the HPO (the location may change according to the operational needs: this must be always updated)
- Indication of the responsible person in charge of the device/equipment
- Utilisation status, including the due date for calibration, preventive maintenance, maintenance history
- Availability and possible expiry dates for consumables (usually up to 5 years and indicated on the MD packaging)
- Total incurred costs for purchasing, maintenance and operation feeding the evaluation of the total cost of ownership
- Warnings about security and risk issues

6.2.3 Reprocessing

For some applications, the HPO might be involved in the reprocessing of devices. It is e.g. the case of cleaning and disinfection/sterilisation of surgical tools or endoscopy equipment.

According to ISO 17664:2017 [10], the reprocessing is the set of activities to be undertaken on a (reusable) medical device to achieve (depending on the operational needs):

- Cleaning, i.e. "removal of contaminants to the extent necessary for further processing or for intended use"
- Disinfection, i.e. "process to reduce the number of viable microorganisms to a level previously specified as being appropriate for a defined purpose"
- Sterilisation, i.e. "process used to render the product free from viable microorganisms"

Both FDA (Food and Drug Administration in the USA) and EU-MDR (European Union Medical Device Regulation) [11] clearly state the conditions for the reprocessing of the medical devices.

Following the definition given in EU-MDR, reprocessing is intended as:

> *process carried out on a used device in order to allow its safe reuse including cleaning, disinfection, sterilisation and related procedures, as well as testing and restoring the technical and functional safety of the used device.* (Article 2(39) of [10])

In recent years, the generalised tightening of the health budgets has also started the interest for the reuse of devices, even if intended for single use. This practice may in principle not be strictly forbidden, provided that the reprocessing is performed according to specific rules that ensure the device keeps its characteristics in terms of efficacy and safety. In this case, however, the responsible for the reprocessing of the Single-Use Device (SUD) assumes the role a *new manufacturer* of the device and bears all the responsibilities for the performed process. The process should, of course, also include the required quality control steps.

At the basis of this procedure is the evidence that the applied process is scientifically proven and validated to ensure that the reconditioned device can be cleaned, disinfected, functionally tested and reused without any harm for the patients and caregivers.

Patients and healthcare professionals should be granted that the reused device has the same performance and safety margin of a new one.

Whilst the HPO tries to cut cost through the reprocessing of SUDs, the manufacturers are usually not supporting this practice. This may not always be due only to the desire to increase sales, but is also due to purely technical reasons. In most cases, the reprocessing procedure, if not properly performed, may alter the characteristics of the device in an uncontrollable way.

The reuse procedure of many medical device is performed with hazardous chemicals like peracetic acid (CH_3COOOH), sodium hypochlorite (NaOCl) and hydrogen peroxide (H_2O_2). They might damage the components of the device and cause adverse reaction both in patients and operational staff.

The HPO should also be aware of the cost of the overall reconditioning procedure. The cost of quality management for the properly performed reuse procedure may even be higher than the expected cost savings.

Due to economy of scale in production, single-use devices have become cheaper than the overall cost for reconditioning of devices as well as the education of staff for the reuse procedure.

6.3 Impact on the Healthcare Processes

In recent years, the quest for quality and efficiency in healthcare has stimulated the application of process management strategies in many healthcare organisations [12–14].

It is possible to identify five main processes involved in the delivery of healthcare [14] and in the creation of value for patients and the community:

- Keeping people healthy (prevention) and provide a good quality of life
- Detecting health problems
- Diagnosing diseases
- Treating diseases

Chapter 1 gives an overview of the contribution of the medical device technology to the above processes.

The widespread application of medical devices and equipment, besides the impact it has on the infrastructure, requires the adaptation of all processes to the new technology.

This is of particular importance when considering the high rate of innovation characterising the medical device field.

It is important to remark that the pervasive introduction of medical devices and complex pieces of equipment in the HPOs requires a careful management of all the involved risks.

Risk control becomes, then, an even more important aspect of the activities to ensure the success of the healing process.

6.3.1 The Concept of Risk in Medical Devices

It is well known that every medical act is connected with risk. The very term *pharmaceutical* derives from the Greek φάρμακον—*phármakon* that has itself the double valence of remedy (medication) and poison.

Even if it is impossible to eliminate all risks from any human activity, the user of medical devices must consider the need to manage these risks and clearly understand the level of the *risk/benefits* ratio connected to the use of the device. Moreover, the acceptability of the level of risk vs. the benefits might be strongly subjective and strictly linked to the cultural position of the served community.

A Risk Is Not a Disease

It's worth to remind that a risk refers to something at the horizon that may or may not happen. The point is how to manage it.

With all the above in mind, the stakeholders involved in the production and use of the medical devices must put in force a risk management process to reduce the risks at a technically and ethically acceptable level and agreed by the served community.

The French mathematician and philosopher Blaise Pascal (1623–1662) gave one of the former definitions of risk:

> *Risk should be proportional to the probability of occurrence as well as to the extent of damage.*

This definition can be translated in mathematical terms as:

$$R = p * C$$

where p is the likelihood of an event and C the consequence of this event.

This is the standard definition, also adopted by ISO 14971 [15], that defines the risk as the combination of the *probability* of occurrence of a *harm* and the *severity* of that *harm*.

This means that the risk management must act on the probability of harm and on the possible consequences.

The stakeholders involved in the design, distribution and use of a MD must then take all technical and managerial actions to shape p and C during the overall device life cycle.

This can be achieved setting-up a risk management plan aiming at:

- ***Risk assessment***: Identification and evaluation of the risks connected with the different phases of the device life cycle
- ***Risk control***: Identification and implementation of the measures needed to reduce this risk

As recalled above, it is impossible to eliminate all possible risks from any human activity, and especially from medical acts. This means that every device will be characterised by a *residual risk* (defined in ISO 14971 15 as "*the risk remaining after all the risk control measures have been implemented*").

The *residual risk* is then the key information allowing the physician or the clinical expert to evaluate the benefits and the hazardous situation that may arise in the clinical practice when using the device.

Discussing about risk there are few more considerations to be added.

First is the fact that the evaluation of the *acceptable level of risk* might be strongly subjective and it is highly influenced by cultural standpoints and specific operational situations.[7]

Second, that in the evaluation of risk the possibility of user's errors and the *reasonably foreseeable misuse*,[8] either intentional or unintentional, should be included.[9]

6.3.2 The Risk Management Activity in HPO

The above discussion highlights the risk management among the most important processes that take place in HPO, especially when dealing with medical devices and equipment.

The risk assessment and the risk control should consider the environment and the organisational context in which the device or equipment is used. This should consider, as reminded by [16], all aspects like: "*transport, hospital use, home use, backup systems, interaction with other devices and systems, impact of multiple device environments or multiple device use*".

The risk assessment should include also the possible risk due to the loss of benefit in case of device's malfunctioning or unavailability. This activity requires a deep knowledge of different aspects, including (but not limited to) current clinical

[7] Risk acceptability is strongly influenced by the society's tolerance of risk and by the conditions in which the device is used (routine, emergency or optional therapy).

[8] Defined in ISO 14971 [15] as the use of the device in a way not intended by the manufacturer, but that can result from predictable human behaviour.

[9] One example of intentional misuse is the reuse of a single-use item (without the adequate reconditioning, see Sect. 6.2.3). To possibly prevent this, the manufacturer should give clear indication of the potential harm that this practice may generate.

practice, alternative product and procedures and possible expected changes in clinical practice.

The risks connected to the medical device are usually including physical (e.g. mechanical, electrical, thermal), chemical, radiation or biological harms.

The risk level is very much depending on the user's interaction with the device, and specific provisions must be included in the standard operating procedures (SOPs) to avoid, or minimise, this risk.

The interaction of the user with the device is strongly influenced not only by the design of the device itself, but also on the application environment, that may be a main source of errors [17–19]. The additional risk factors may arise, among others, from user's error or from any device malfunctioning or unavailability, possibly created by wrong or incorrect maintenance or shortage of required consumables. These risks, that are above the *baseline risk profile*[10] of the device itself, shall be considered in the evaluation of the overall risk profile of the HPO operations [16].

J. Reason, making reference to his *Swiss cheese model* [20] recalls the fact that a consistent risk control in a healthcare institution must consider and assess the overall risk involved on top of the baseline risk profile for a given device/equipment. This assessment includes all the possible aspects that may harm the ability of the caregivers to deliver the correct treatment.

It is reported in the literature [20] the case of a fatal outcome due to the wrong calibration of a morphine delivery infusion pump.

The error was generated by the fact that the hospital adopted two kind of infusion pumps with different calibration (mL/day and mL/h, respectively). During the syringe change the nurse applied the calibration in mL/day on a pump that should be calibrated on mL/h. This resulted in a lethal overdose.

The lesson learned by this example is that these kinds of incident can be avoided, or their probability reduced, if the **overall** system is designed to consider the possible errors in the operation of the medical device.

Adequate staffing in order to avoid the hectic generated by personnel overload and careful consideration in the device procurement and personnel training are the key factors to reduce the risks.

[10]The white paper AAMI Risk Principles/2015-08-25 defines the Baseline Risk Profile as the premarket estimation of the actual residual risk from using a properly designed, manufactured and labelled medical device [16].

6.4 A Possible Paradigm: The Case of Blood Purification with Haemodialysis

6.4.1 Short Intro

Haemodialysis (HD) is a life-saving treatment required when a patient has lost, completely or to a major extent, his renal functions. It aims at the purification of the blood from the toxic retention solutes produced by the metabolic processes and in addition at the elimination of excess fluid accumulated in the body.

The treatment is performed with the use of a medical equipment (the artificial kidney) connected to the single patient, equipped with a dedicated set of consumables and supplied with water containing acid and basic concentrates. The treatment consists in taking the blood from the forearm vein of the patient. The blood is guided with a pump through the extracorporeal blood circuit that includes a filter (*dialyser*). The blood flow is usually between 200 and 500 mL/min.

An isotonic fluid (*dialysis fluid*) flows (usually at 500 mL/min or more) in the filter, in the opposite direction of the blood, and provokes the removal of uremic retention products from the blood.

The artificial kidney causes also the removal of excess fluid by the application of a controlled pressure gradient across the dialysis filter with the help of a dedicated pump.

A simplified diagram is shown in Fig. 6.5, where are also indicated the main parts of the artificial kidney and the monitoring and control subsystems.

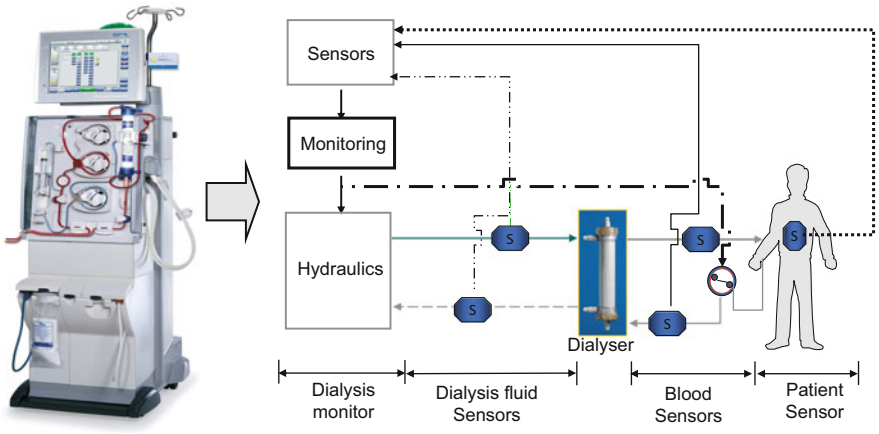

Fig. 6.5 Example of haemodialysis treatment and picture of an artificial kidney system (*5008 Cordiax from Fresenius Medical Care*). The sensors (S) and monitoring system guarantee that all the physiological parameters are kept within the required and safe values and can also give indications about the achievement of the treatment targets. (Adapted from [21]—courtesy of Fresenius Medical Care for the dialysis monitor picture)

The HD treatment requires the careful organisation of the infrastructure and processes supporting it and can be considered as a useful paradigm/model to exemplify the considerations given above.

6.4.2 Operations

The HD treatment is performed (usually) three times a week and lasts about 4 h. During the treatment, the patient should lie on a bed or sit on a special chair.

The treatment is performed in a dedicated area that must be designed and equipped to ensure the safety of patients and personnel, efficiency of the operations and patient's comfort.

As mentioned above, the treatment requires the use of dedicated consumables such as needles, filters, blood lines and chemical products (concentrates) which require to be stocked, taken to the patient's treatment place and discarded with the appropriate procedure after the treatment.

The treatment system requires to be supplied with highly purified water that is prepared onsite. Water usually comes from the municipal water supply network and passes through a water purification system. This system is based on a reverse-osmosis equipment and is implemented onsite according to the need of the centre, e.g. the amount of required water and in relation to the characteristics of the tap water available. The reverse-osmosis device and the parts in contact with the purified water fed to the treatment system are considered medical devices. The water purification system requires a specific design, validation, commissioning, dedicated maintenance and periodic monitoring of the water quality according to the applicable international standards and/or country specific regulations [21].

6.4.3 Infrastructure

The dialysis treatment identifies a specific set of requirements for the infrastructure where the treatment is performed (dialysis centre, dedicated area in a general hospital or in a patient's home).

The presence of the medical equipment and devices dedicated to the dialysis treatment generate some distinctive characteristics[11] for the building where the treatment is performed with respect to other ambulatory facilities [22].

Besides the need to allow for the easiest and most efficient patients- and personnel-flow, a specific set of requirements are:

[11] Here are considered only the features relevant to the application of the dialysis related medical devices/equipment. In addition, all general considerations for the design of a facility for ambulatorial medical practices are applicable.

- A reserved area where the treatment is performed, equipped with:
  - Dedicated electric power supply for the dialysis monitor, separated from other users.
  - Supply of purified water.
  - Drain pipe for waste fluids coming from the dialysis system that are potentially contaminated by biological waste products, chemicals and disinfecting agents. A possible purification system before discarding them in the public sewage network might be required.
  - Provisions for medication preparation and for hygiene procedures for patients and staff, e.g. handwashing stations.
  - Surveillance desk allowing the personnel to watch the patients under treatment and see the possible alarm signal from the dialysis system.
  - Adequate space to accommodate the patient (on bed or chair) and the artificial kidney, with space for access by the caring staff doing treatment, monitoring (e.g. blood pressure measurement) and for emergency operations.
- Large stock areas for consumables (e.g. fistula needles, blood lines, dialysis filters, concentrate containers)
- Separated area for the disposal of the used consumable items (potentially contaminated)
- Dedicated area for the water treatment system

From the above considerations, it appears that the design of the infrastructure of a facility delivering dialysis treatment requires a set of provisions that are strongly related to the presence of the specific medical equipment used: in particular the dialysis- and the water treatment-system.

Table 6.1 (modified and adapted from [22]) shows the specific requirement to the building.

Besides the impacts on the physical infrastructure, the artificial kidney operation requires the organisation of other aspects as summarised in Fig. 6.2.

One important aspect is the availability of an adequate ICT facility. The workflow and the treatment results can be dramatically improved when all dialysis monitors are connected to a central network where all the patients' data are collected, stored and monitored. These data may include the parameters gathered during the treatment by any ancillary medical devices, like blood pressure and temperature monitoring. This information system can also improve the efficiency in the management of the consumables.

The safe and effective operation of the treatment requires the presence of dedicated and trained staff and the clear definition of the responsibility of each operator.

This covers the presence of the medical personnel directly involved in the treatment: mainly physicians for the prescription and supervision of patient's status and trained nurses performing the treatment itself. In addition, trained technicians take care of the continuous maintenance of dialysis equipment and water treatment system [9, 19]. These personnel may also be outsourced, but it should be ready-available for any emergency need.

Table 6.1 The specific characteristics of an HPO infrastructure performing haemodialysis (adapted from 22)

Function	Purposes	Requirements
Dialysis treatment area	Performance of dialysis treatment	Space for the accommodation of dialysis equipment and required supplies
Water treatment room	Allocate the equipment for the preparation and distribution of purified water (dialysis water)	Space to allow the positioning of equipment and the easy maintenance and monitoring
Consumable stock area	Stock of consumable for dialysis treatment (and other medication items)	Temperature and humidity control (as for general pharmaceutical products) Easy access and communication to treatment area
Used consumable disposal area	Allocate the waste products (spent consumables)	Easy access and communication with treatment area and for collection from outside Separation of contaminated waste
Drain fluids treatment	Treatment of discarded fluids (e.g. spent dialysis fluid) before the collection by the public waste fluids system	In some location (depending on the country regulations) the law requires the purification of the discarded fluids from dialysis must be purified from disinfecting agents, pharmaceuticals or excessive biological waste products [23][a]

[a]In some situations, equipment for fluid treatment for water reuse may be foreseen

6.5 Additional Considerations for Low-Income Countries

The use of complex medical devices in low-income countries deserves few additional considerations (see also Chap. 12).

Whilst it is an obvious advantage to allow the populations of poor rural areas to access the most advanced diagnostic and therapeutic solutions, possibly based on complex medical equipment, it is important to ensure preventively that all the technical and logistic prerequisites are in place.

According to [24], between 25 and 35% of the medical devices in the so-called low-income countries are out of order or heavily underused due to lack of maintenance or unavailability of spare parts and consumables.

In addition, the lack of adequate resources reinforces the temptation to reuse disposable items meant for single use and possibly recondition them following cheap but inadequate procedures. This, of course, contribute to worsen the situation and may generate additional risks or bad outcome for patients.

All the above issues may frustrate the efforts done to build a better healthcare system in these countries.

The installation of complex medical equipment, sometimes with the help of donations, should always be completed with the adequate infrastructure, the training

to create the technical competence in loco as well as all the logistic organisation to ensure the timely availability of required consumables with adequate quality.

The organisations developing, producing and selling medical devices and equipment should carefully consider the above aspects. Very performant and expensive products may not be useful in lower-income countries or in remote rural areas without adequate resources. Under these conditions, the required expenditure cannot be afforded and the proper operation and maintenance cannot be ensured. This means that manufacturers should also focus on products that, even if assuring the adequate level of care, quality and safety, are simpler, less expensive and easy to use. This will be one of the most important challenges for the future of the medical device industry.

Conclusion

The introduction of medical devices and equipment of different complexity has an important impact on the structure and on the process of a healthcare provider organisation.

Main impacts on the infrastructure are:

- The physical layout should be designed in order to allow the safe and effective use of the devices. This is to guarantee the smooth workflow allowing for the access of patients and personnel as well as for the delivery and internal distribution of consumables and the disposal of spent single-use devices.
- The facility allows the allocation of specific equipment in dedicated areas (e.g. water treatment system).
- The risk management strategies should be adapted to include the operation of the medical devices and their specific requirements (e.g. the presence of strong magnetic fields in the area where the MRI equipment is installed).

The availability of trained personnel and the clear allocation of responsibilities is mandatory. This may include the presence of a bioengineering/technical department (at least for larger structures) taking care of all the technical issues, e.g. assistance for procurement, commissioning, maintenance, decommissioning.

The use of medical equipment in low-income countries requires a holistic approach focusing on properly designed equipment, its maintenance, the availability of affordable consumable material and the training of personnel *in loco*.

Take Home Message

– In the Healthcare Provider Organisation, the successful application of the medical technologies requires the adoption of a systemic view of the different elements influencing the quality of delivered care. Key factors are infrastructure and processes, training of operators and well-allocated responsibilities.
– The task of the decision makers is to concentrate on the different phases of the medical devices/equipment life cycle, from the acquisition and

(continued)

commissioning to the disposal, to ensure that the quality of the delivered care, the appropriate use of the resources and the best return of the financial investment are achieved.
- The risk management is among the most important topics when considering the healthcare processes related to the extensive use of medical devices and equipment of different complexity.
- The estimation and control of the Total Cost of Ownership (TCO) is a very important management tool. Apart from the pure purchasing cost, the TCO analysis also allows to spot the hidden costs that, on top of the purchasing price, may arrive at up to 85% of the total cost during the overall device's life cycle.
- The application of medical technology in low-income countries deserves the careful consideration of the aspect related to the equipment design and maintenance, the availability of the required infrastructure and consumables as well as the establishment of adequate operators' training.

References

1. De Savigny D, Adam T (eds) (2009) Systems thinking for health systems strengthening. World Health Organization, Geneva
2. WHO Medical Device Technical Series (2011) Procurement process resource guide. World Health Organization, Geneva
3. Dorval M, Jobin M (2018) Towards better quality in healthcare and operations management: a developmental literature review. Proc 23rd Int Conf Inf Qual 12(2):254–263
4. Ibn H, Haj E, Lamrini M, Rais N (2008) Quality of care between Donabedian model and ISO 9001. Int J Qual Res 7(1):17–30
5. Scholz S, Ngoli B, Flessa (2015) Rapid assessment of infrastructure of primary healthcare facilities—a relevant instrument for healthcare systems management organization, structure and delivery of healthcare. BMC Health Serv Res 15(1):1–10
6. WHO (2003) Medical device regulations global overview and guiding principles. World Health Organization, Geneva
7. Lehoux P (2006) The problem of health technology. Routledge Taylor & Francis Group, LLC, New York
8. Webster A (2007) Health, technology and society. Palgrave Macmillan, Basingstoke
9. ISO 23500-1 (2019) Preparation and quality management of fluids for haemodialysis and related therapies—part 1: general requirements. International Organization for Standardization
10. ISO 17664 (2017) Processing of healthcare products—information to be provided by the medical device manufacturer for the processing of medical devices. International Organization for Standardization
11. REGULATION (EU) 2017/745 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC
12. Hellström S, Lifvergren S, Quist J (2010) Process management in healthcare: investigating why it's easier said than done. J Manuf Technol Manag 21(4):499–511
13. Müller R, Rogge-Solti A (2011) BPMN for healthcare processes. In: Proceedings of the 3rd Central-European workshop on services and their composition. Karlsruhe, Germany, pp 58–64

14. Bergman B, Neuhauser D, Provost L (2011) Five main processes in healthcare: a citizen perspective. BMJ Qual Saf 20(Suppl. 1):2010–2011
15. ISO 14971:2019 Medical devices—application of risk management to medical devices
16. AAMI White Paper (2015) Risk principles and medical devices: a postmarket perspective association for the advancement of medical instrumentation Arlington
17. C.N. Recommendations (2000) Applying human factors and usability engineering to medical devices guidance for industry and Food and Drug Administration staff additional copies, no. 301
18. Reason J (2000) Human error: models and management. Br Med J 320(7237):768–770
19. Marcelli D, Parisotto MT, Soley I, Bedenbender-Stoll E, Scatizzi L, Boccato C, Stopper A, Gatti E (2009) Gestione del rischio nelle organizzazioni sanitarie: l ' esempio di NephroCare. Giornale Italiano di Nefrologia 26(6):719–728
20. James R, Carthey J, de Leval MR (2001) Diagnosing 'vulnerable system syndrome': an essential prerequisite to effective risk management. Qual Heal Care 10(Suppl. 2):ii21–ii25
21. Boccato C, Evans D, Lucena R, Vienken J (2015) Water and dialysis fluids. PABST Science Publishers, Langerich
22. Merello de Miguel M, Boccato C, Giordana G (2007) Dialysis centres an architectural guide. PABST Science Publishers, Langerich
23. Tarrass F, Benjelloun M, Benjelloun O (2008) Recycling wastewater after hemodialysis: an environmental analysis for alternative water sources in arid regions. Am J Kidney Dis 52(1):154–158. https://doi.org/10.1053/j.ajkd.2008.03.022
24. WHO (2010) Medical devices: managing the mismatch background paper 5: context dependency of medical devices. Prior Med Devices, World Health Organization, Geneva

Chapter 7
Information and Communication Technology: Implications on Patient's Privacy and Security

Giovanni Calcagnini, Federica Censi, and Eugenio Mattei

Abstract The trend to personalized medical therapies needs the recording, documentation, and surveillance of patient data. Many advanced medical devices are directly linked to sensors and register patient data. Breaching such data may lead to either violations of patient's rights or in the worst case to even eventful therapy mistakes. In Europe, directives have been advanced dealing with "Network and Information Security (NIS)" and the establishment of a competent national NIS authority. In addition, personal data are secured by a new EU regulation since 2016, entitled "General Data Protection Regulation (GDPR)." It includes pseudonymization and encryption of personal patient data. The new Medical Device Regulation of the EU (MDR) which is valid since May 2021 further requires activities on risk management, software life cycle, and information security techniques, actions which all affect the introduction of advanced medical devices and also define responsibilities of manufacturers and healthcare delivery organizations.

The USA take care of data protection through the "Health Information Portability and Accountability Act (HIPAA)." However, there is currently no general federal legislation, rules are sector specific. The FDA further provides guide documents for manufacturers and healthcare delivery organizations to be able to comply with these security provisions.

Introduction

Health data refers to personal information. This includes both medical data, such as health status of a person, doctor referrals and prescriptions, medical examination reports, laboratory tests, and radiographs. This also involves administrative and financial data about health (the scheduling of medical appointments, invoices for healthcare services, medical certificates for sick leave management, etc.). Health data are thus considered sensitive data and are subject to particularly strict rules to

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ensure that the health data are protected and not subject to any unauthorized disclosure or use.

Information and Communication Technology (ICT) and new medical technologies are offering opportunities to collect, store, use, and share health data, but they pose new challenges for privacy and data security. An example is represented by the remote monitoring and follow-up of pacemakers (PM) and implantable cardioverter defibrillators (ICD). In this case, the data downloaded from the device to a transmitter are then sent to the physician, using either the landline phone or the mobile network. Many current PMs and ICDs are able to automatically execute tests on the device, such as battery status, lead impedances, or sensing and capture thresholds. Therefore, remote monitoring has the potential to offer improved patient safety and quality of care. In 2008, Halperin et al. [1] performed laboratory tests on an implantable defibrillator and were able to retrieve unencrypted personal patient data. This report triggered considerable media coverage, even though to date there have been no reports of hacking of implantable devices.

7.1 The Present Status

According to a study published in 2018 in the Journal of the American Medical Association (JAMA) by McCoy and Perlis [2], the most commonly breached information between 2010 and 2017 in the USA was from paper or film. The study accounts for 510 breaches (24%) comprising a total of 3.4 million records (2%). However, the 410 breaches (19%) of information from network servers accounted for the largest share of breached records, 139.9 million (79%). The most commonly breached media locations shifted from laptop and paper or films in 2010 to network servers and e-mails in 2017. Authors concluded that *although networked digital health records have the potential to improve clinical care and facilitate learning health systems, they also have the potential for harm to vast numbers of patients at once if data security is not improved* [2].

In 2019, Jiang and Bai [3] investigated the detailed causes of health information data breach related to 1138 breach cases that occurred from 2009 to 2017 and published by the US Department of Health and Human Services. They found that that more than half of the cases were not from external causes but were attributable to internal mistakes or neglect. Mobile devices were involved in 46% of cases, while paper records accounted for just 29% of breaches, as the researchers report in JAMA Internal Medicine. Employees taking data home or forwarding it to personal email accounts contributed to 74 breaches in the study, i.e., about 6.5% of cases.

Thus, to date most health information data breaches in the USA in recent years have not been the work of hackers but instead have been due to mistakes or security lapses inside healthcare organizations and operators.

Yet the potential harm of hacker attacks was made clear when on May 12, 2017 the UK National Health System (NHS) was infiltrated by a ransomware worm known as “WannaCry.” Whole hospital and primary care networks were affected

and suspended, and the NHS went into complete electronic lockdown. WannaCry's infection became the biggest cyberattack on critical infrastructure in UK history [4].

Over the last years, many countries have enacted or strengthened data privacy laws. To date, 132 countries have data privacy laws in force.

At worldwide level, it is important to refer to the Medical Device Cybersecurity Guide under development by a Working Group of the International Medical Device Regulators Forum (IMDRF). The purpose of this initiative is to promote a globally harmonized approach to medical device cybersecurity and to provide medical device cybersecurity guidance for stakeholders across the device life cycle.

The European Union Agency for Cybersecurity, ENISA, is the Union's agency dedicated to achieving a high common level of cybersecurity across Europe. Established in 2004 and strengthened by the EU Cybersecurity Act [5], the European Union Agency for Cybersecurity contributes to EU cyber policy, enhances the trustworthiness of ICT products, services and processes with cybersecurity certification schemes, cooperates with Member States and EU bodies and helps Europe to prepare for the cyber challenges of tomorrow.

In Europe, the following legislative acts are relevant to the cybersecurity of medical devices or to operators dealing with protecting or processing of personal data stored in medical devices and might apply in parallel to the medical devices' regulations:

- Network and Information Security (NIS) Directive [6]
- General Data Protection Regulation (GDPR) [7]

The NIS Directive provides legal measures to boost the overall level of cybersecurity in the EU by ensuring:

- Member States preparedness by requiring them to be appropriately equipped, e.g., via a Computer Security Incident Response Team (CSIRT) and a competent national NIS authority.
- Cooperation among all the Member States, by setting up a cooperation group, in order to support and facilitate strategic cooperation and the exchange of information among Member States.
- A culture of security across sectors which are vital for economy and society and moreover rely heavily on ICT, such as energy, transport, water, banking, financial market infrastructures, healthcare and digital infrastructure. Key digital service providers (search engines, cloud computing services, data storage services, and online marketplaces) will have to comply with the security and notification requirements under the new Directive.

In May 2016, the European Union adopted a new Regulation (EU) 2016/679 on the protection of personal data (GDPR—General Data Protection Regulation). It was designed to replace the 1995 Data Protection Directive 95/46 EC. Although the key principles of data privacy still hold true to the previous directive, many changes have been proposed to the regulatory policies. The GDPR protects personal data regardless of the technology used for processing that data. It's technology neutral and

applies to both automated and manual processing, regardless how the data is stored (e.g., IT system, through video surveillance, or on paper).

After GDPR publication, numerous countries have also updated their data protection laws, invariably strengthening them in ways, which reflect some aspects of the GDPR [8].

7.2 EU: The General Data Protection Regulation (GDPR)

The abovementioned GDPR regulates the processing by an individual, a company, or an organization of personal data relating to individuals in the EU. Personal data is any information that relates to an identified or identifiable living individual.

Article 5 of GDPR outlines six data protection principles:

- Lawfulness, fairness, and transparency
- Purpose limitation
- Data minimization
- Accuracy
- Storage limitation
- Integrity and confidentiality

The integrity and confidentiality principle is the only one related to data security: data shall be processed in a manner that *ensures appropriate security of the personal data, including protection against unauthorized or unlawful processing and against accidental loss, destruction or damage, using appropriate technical or organizational measures*. GDPR does not indicate specific technical measure to ensure integrity and confidentiality, because technological and organizational best practices are constantly changing.

GDPR considers health data as a special category of personal data. According to Art. 9, the processing of data related to health is prohibited unless one or more of the conditions laid down in § 2 apply. These conditions include:

- Explicit consent given by the subject to process his/her data for one or more specific purposes
- Processing necessary to protect the vital interests of the data subject or of another natural person where the data subject is physically or legally incapable of giving consent
- Processing for preventive or occupational medicine by or under the responsibility of a professional subject to the obligation of professional secrecy
- Processing for reason of public interest in the area of public health (e.g., protection against serious cross-border threats)

Member States may maintain or introduce further conditions, including limitations, with regard to the processing of genetic data, biometric data, or data concerning health.

Article 32 of GDPR outlines the measures to be taken to protect personal information. Companies shall implement appropriate technical and organizational measures to ensure a level of security appropriate to the risk, including inter alia as appropriate:

- The pseudonymization and encryption of personal data
- The ability to ensure the ongoing confidentiality, integrity, availability, and resilience of processing systems and services
- The ability to restore the availability and access to personal data in a timely manner in the event of a physical or technical incident
- A process for regularly testing, assessing, and evaluating the effectiveness of technical and organizational measures for ensuring the security of the processing

In the case of a personal data breach, the organization, not later than 72 h after having become aware of it, shall notify the personal data breach to the supervisory competent authority, unless the personal data breach is unlikely to result in a risk to the rights and freedoms of natural persons.

7.2.1 Pseudonymization and Encryption

The GDPR specifically requires encryption or pseudonymization of personal data and does not require breach disclosure to subjects, if the breached data is encrypted.

Pseudonymization means the processing of personal data in such a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information. Such additional information must be kept separately and is subject to technical and organizational measures to ensure that the personal data are not attributed to an identified or identifiable natural person.

Data encryption converts data into another form, or code, so that only people with access to a secret cryptographic key can read it. The data encryption solution relies on the control placed around the secret cryptographic key, rather than on the original data. Therefore, protection of the cryptographic key is a critical aspect of the encryption.

7.2.2 The Right to be Forgotten

Article 17 of GDPR introduces a novel element that may require significant effort to be fulfilled. This article stipulates that organizations must erase a data subject's records upon request "without undue delay" where there is no compelling reason to keep them on hand. If the organization has shared the requestor's data externally, it must also notify other data controllers that the data subject has requested the erasure.

The implementation of the technical standard ISO 27001 covers most of the requirements of the GDPR. Some further measures will have to be included in order to ensure compliance with the EU GDPR, such as:

- Procedures for ensuring the exercise of the rights of data subjects (e.g., right to be forgotten)
- Mechanisms for the transfer of data outside the EU
- Minimum content of the impact assessment on data protection
- Procedures to be followed in case of violation of personal data

7.3 EU: Information Security and IT for Medical Devices

Several requirements associated with data protection are not explicitly mentioned in the Medical Device Regulation (e.g., requirements regarding privacy and confidentiality of data associated with the use of MDs) since that may be outside the scope of the Medical Device Regulation (MDR), with some exceptions outlined below.

Information security and IT security are addressed explicitly in Annex I, articles 17.2 and 17.4 of the Medical Device Regulation. In addition, Annex I section 1 (general requirements) of the Medical Device Regulation requests that any risks associated with the operation of medical devices must be acceptable so as to enable a high level of protection of health and safety. To this end, there is a need to consider the relationship between "safety and security" (see also Chap. 6) as they relate to risk, since safety may be compromised due to "security issues" which may have "safety impacts" (Medical Device Coordination Group—MDCG 2019-16 Guidance on Cybersecurity for medical devices) [9].

In particular in the context of information security and within the MDR, the manufacturer should be particularly aware of the following provisions:

- Privacy and data protection: Article 62.4(h): General requirements regarding clinical investigations conducted to demonstrate conformity of devices
- Conformity assessment procedures: Article 52
- Post-market surveillance system of the manufacturer: Article 83
- Post-market surveillance plan: Article 84
- Post-market surveillance report: Article 85
- Periodic safety update report: Article 86
- Reporting of serious incidents and field safety corrective actions: Article 87
- Trend reporting: Article 88
- Analysis of serious incidents and field safety corrective actions: Article 89
- Technical documentation: Annex II
- Technical documentation on post-market surveillance: Annex III
- Clinical evaluation and post-market follow-up: MDR Chapter VI and Annex XIV

The Guidance on Cybersecurity for medical devices provides manufacturers with guidance on how to fulfil all the relevant essential requirements of Annex I of the MDR with regard to cybersecurity.

Harmonized and International Technical Standards may be used to demonstrate the compliance with the MDR security requirements. To date, the relevant standards in this field are:

- EN ISO 14971 Risk Management
- EN 62304 Software Lifecycle and IEC 82304-1 Health Software Part 1: General requirements for Product Safety
- EN ISO/IEC 27000 Information technology—Security techniques—Information security management systems (ISMS)—Overview and vocabulary and EN ISO/IEC 27001 Information Technology—Security techniques – Information Security management Systems—Requirements.
- ISO/IEC 80001-1 Application of Risk Management for IT networks Incorporating Medical Devices, and the associated particular standards: ISO/IEC 80001-5-1 Application of Risk Management for IT networks incorporating medical device—Safety, effectiveness and security in the implementation and use of connected medical devices or connected health software—Part 5-1: Activities in the product life cycle. IEC/TR 80001-2-2 Application of Risk Management for IT networks Incorporating Medical Devices Part 2-2: Guidance for the Disclosure and Communication of Medical Device Security Needs, Risks and Controls.
- EN ISO 62366 / ISO 60601-4 Usability Engineering
- IEC/TR 60601-4-5 Medical Electrical Equipment—Part 4-5. Safety related technical security specifications for medical device

7.4 The USA: The Health Information Portability and Accountability Act

In the USA, there is no general federal legislation, but there are federal data protection laws, which are sector specific. The Health Information Portability and Accountability Act (HIPAA) provides data privacy and security provisions for safeguarding medical information. Title II of HIPAA directs the US Department of Health and Human Services (HHS) to establish national standards for processing electronic healthcare transactions. It also requires healthcare organizations to implement secure electronic access to health data and to remain in compliance with privacy regulations set by HHS. Title II includes the following HIPAA compliance requirements:

- HIPAA Privacy Rule. Officially known as the Standards for Privacy of Individually Identifiable Health Information. This rule establishes national standards to protect patient health information.

- HIPAA Security Rule. The Security Standards for the Protection of Electronic Protected Health Information sets standards for patient data security.

In HIPAA documentation, any organization or corporation that directly handles electronic protected health information (ePHI) is referred to as a *covered entity*. All covered bodies, including hospitals, physicians' offices, and health insurance providers must abide by HIPAA Security Rule guidelines when handling ePHI. According to the HIPAA Security Rule, covered entities must ensure the confidentiality, integrity, and availability of all ePHI they create, receive, maintain, or transmit. This includes identifying and protecting against reasonably anticipated threats to the security or integrity of the information.

To support the appropriate activity planning of covered entities, the HIPAA Security Rule specifies a series of administrative, technical, and physical security procedures to assure the confidentiality, integrity, and availability of ePHI.

The Food and Drug Administration (FDA) provides guides to address cybersecurity issues in medical devices [10]. Medical device manufacturers (MDMs) and healthcare delivery organizations (HDOs) should take steps to ensure appropriate safeguards are in place.

- Medical device manufacturers (MDMs) are responsible for remaining vigilant about identifying risks and hazards associated with their medical devices, including risks related to cybersecurity.
- Healthcare Provider Organizations (HPOs) should evaluate their network security and protect their hospital systems.
- Both MDMs and HPOs are responsible for putting appropriate mitigations in place to address patient safety risks and ensure proper device performance.

Conclusion

The trend to personalized medical therapies requires the recording, documentation, and surveillance of patient data. Many advanced medical devices are directly linked to sensors and register patient data on, e.g., patient cards or device internal storage files. Breaching such data may lead to either violations of patient's rights or in the worst case to even eventful therapy mistakes. In Europe, directives have been advanced dealing with "Network and Information Security (NIS)" and the establishment of a competent national NIS authority. In addition, personal data are secured by a new EU regulation since 2016, entitled "General Data Protection Regulation (GDPR)." It includes pseudonymization and encryption of personal patient data. It must be emphasized that an officially published regulation has the status of a law in European countries. The new Medical Device Regulation of the EU (MDR) which is valid since May 2021 further requires activities on risk management, software life cycle, and information security techniques, actions which all affect the introduction of advanced medical devices and also define responsibilities of manufacturers.

The USA take care of data protection through the "Health Information Portability and Accountability Act (HIPAA)." However, there is currently no general federal legislation, rules are sector specific. The FDA further provides guide documents for

manufacturers and healthcare delivery organizations to be able to comply with these security provisions.

Finally, both medical device manufacturers and healthcare provider organizations are challenged to comply with these regulations. It is recommended to consider such regulations during the whole life cycle from the early conceptual phases of medical devices, during clinical application and subsequent market surveillance.

Take Home Message

- Personalized medical therapies often require the recording of patient data on internal storage of the devices.
- Possible breaching of information must be avoided in order to guarantee correct use of data and avoid adverse events such as in the worst case eventful therapy mistakes.
- Both, the EU and the USA have introduced legislation for data protection at a general level and in medical device field, as documented in the EU Medical Device Regulation (MDR) and the "US Health Information Portability and Accountability ACT (HIPAA)."
- Medical device manufacturers and healthcare provider organizations must comply with these regulations during the whole life cycle of a medical device.

References

1. Halperin D et al (2008) Pacemakers and implantable cardiac defibrillators: software radio attacks and zero-power defenses. In: Proceedings of the 2008 IEEE symposium on security and privacy, Oakland, CA
2. McCoy TH, Perlis RH (2018) Temporal trends and characteristics of reportable health data breaches, 2010–2017. JAMA 320(12):1282–1284
3. Jiang JX, Bai G (2018) Evaluation of causes of protected health information breaches. JAMA Int Med 179(2):265–267. https://doi.org/10.1001/jamainternmed
4. Clark R, Youngstein T (2017) Cyberattack on Britain's national health service—a wake-up call for modern medicine. N Engl J Med 377:409–411
5. Regulation (EU) 2019/881 of the European Parliament and of the Council of 17 April 2019 on ENISA (the European Union Agency for Cybersecurity) and on information and communications technology cybersecurity certification and repealing Regulation (EU) No 526/2013 (Cybersecurity Act)
6. Directive (EU) 2016/1148 of the European Parliament and of the Council of 6 July 2016 concerning measures for a high common level of security of network and information systems across the Union. https://ec.europa.eu/digital-singlemarket/en/network-and-information-security-nis-directive

7. Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (Text with EEA relevance). https://ec.europa.eu/info/law/law-topic/dataprotection/reform/what-does-general-data-protection-regulation-gdpr-govern_en
8. Greenleaf G (2019) Global data privacy laws 2019: 132 national laws & many bills. Privacy Laws Business Int Rep 157:14–18
9. Medical Device Coordination Group Document MDCG 2019-16. Guidance on cybersecurity for medical devices. https://ec.europa.eu/docsroom/documents/38941/attachments/1/translations/en/renditions/native. Accessed 20 Jan 2020
10. Food and Drug Administration Cybersecurity. https://www.fda.gov/medical-devices/digital-health/cybersecurity. Accessed Aug 2020

Part IV
Apply Economics in Medicine

Chapter 8
Economic Perspectives: An Overview

Steffen Fleßa

Abstract Economics is the science of describing, explaining, and overcoming scarcity by efficiency. Efficiency compares the outputs and inputs of a system, process, intervention or device, and the knowledge of costs as financial value of the inputs is crucial for avoiding waste of scarce resources. However, calculating the costs is not as simple as it might seem because costs can be tangible and intangible, direct and indirect, core and non-core costs. A thorough analysis of the perspective and the scope of costs is a prerequisite of efficiency and a starting point for the economic evaluation of medical devices.

Introduction

The economic dimension of a medical device plays a major role in its adoption as innovation. *Cum grano salis*, we can state that in particular the costs are the most important single determinant of success and failure of a medical device on the market. If the costs are higher than the revenues, no enterprise will produce or use a medical device, and if the (societal) costs are higher than the benefits of a medical device, the society will not be willing to pay for it. Knowing the costs is crucial for any break-through of medical devices.

8.1 Systems Approach

Figure 8.1 exhibits a simplified business model which is relevant for a wide variety of commodity and service industries, i.e. medical device producers as well as hospitals. Agents of production are transformed into outputs. For instance, a factory uses materials, machines and the expertise of its workers to produce a CT-scanner. This product will be used by the customer (e.g. hospital) to produce a service, i.e. the

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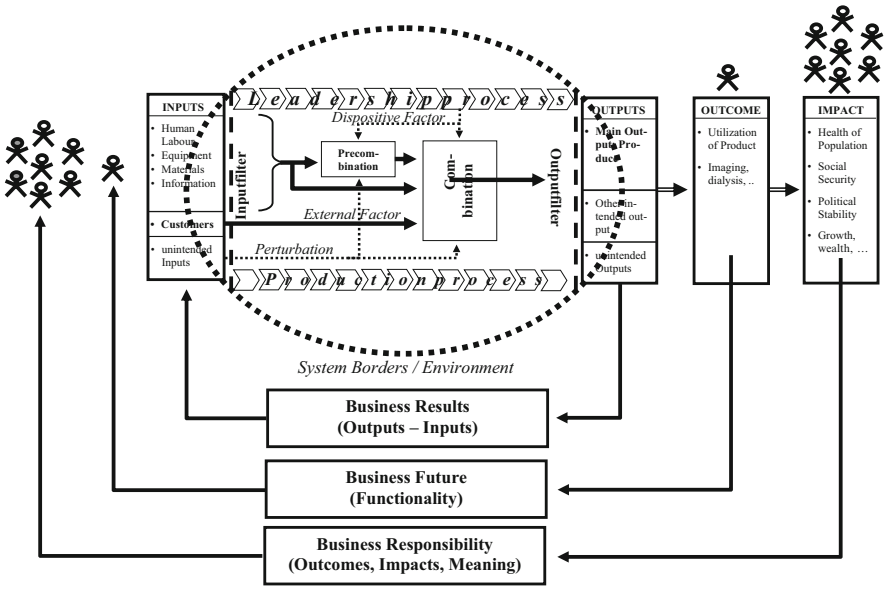

Fig. 8.1 Basic business model, based on [1]

customer experiences an outcome based on the output of the factory. Most likely this imaging will have an impact on the patients and the entire society (health, healing). Consequently, output, outcome, and impact of a product are not identical.

Each business unit has to compare its own output, outcome, and impact with its input of agents of production and its own objectives. The simplest approach is to compare outputs with inputs. The respective quotient is called efficiency, i.e. all business units strive for efficient use of their resources. Efficiency means that a maximum output is generated with a given input or a given output is produced with a minimum of input.

$$\frac{\text{Output}}{\text{Input}} \rightarrow \text{Max!}$$

In addition, any business unit has to compare its outcomes with its inputs and objectives. It is insufficient to produce a commodity or service unless this good has a value for the customer (outcome). The function of any enterprise is to service its customers. Thus, enterprises have to analyse whether the products that they produce fulfill their function. Finally, business units also compare the impact that they have on the wider society with the resources they consume for it. It is their business responsibility to have a positive impact on the society—and the society is only willing to support the business unit with agents of production if it produces worthwhile results.

In this introduction, we will focus on the input-output efficiency. Realistic systems have different inputs (e.g. personnel, materials, equipment) and outputs (e.g. different products); the simple formula must be widened as

$$E = \frac{\text{Outputs}}{\text{Inputs}} = \frac{\sum_{j=1}^{m} w_j * x_j}{\sum_{i=1}^{n} v_i * y_i} \rightarrow \text{Max!}$$

with

x_j	Quantity of output j, $j = 1 \ldots m$
y_i	*Quantity of input i, i = 1 . . . n*
w_j	Weight of output j
v_i	Weight of input i
m	Number of output factors
n	Number of input factors

In principle, any economic evaluation must record all consumption of inputs and all results. Afterwards, inputs and results must be expressed in one dimension so that a performance measurement can be calculated. This fusion of different dimensions to one measurement is very difficult, as hours of labour, kilograms of food, metres of sutures, square metres of space, etc. have to be fused as well as cases, sickness days, death cases, years of life lost, and quality feelings. As most inputs have a market price, the fusion of different resources consumed can be done by using the factor price as input weight. The result is the cost of a service or a programme, i.e.

$$\frac{\sum_{j=1}^{m} p_j * x_j}{\sum_{i=1}^{n} c_i * y_i} \rightarrow \text{Max!}$$

with

x_j	Quantity of result j, $j = 1 \ldots m$
y_i	Quantity of input i, $i = 1 \ldots n$
p_j	Value of one unit of result j
c_i	Costs of one unit of input i [€]
m	Number of result factors
n	Number of input factors

Based on the simple quotient we can ask different guiding questions that allow us to understand the profound business strategies and the role of costs and revenues in making innovative medical devices a success.

- **Inputs**: The analysis has to start with the inputs. Which inputs are used? How can we weigh different inputs in order to bring them in the same dimension (e.g. working hours and kilograms of metal)?

- **Outputs**, **Outcomes**, and **Impact**: Which outputs, outcomes, and impacts are produced? How can we weigh outputs, outcomes, and impacts of medical devices in order to bring them in the same dimension?
- **Quotient**: How do we measure efficiency and performance in different business units? What is the relationship between efficiency, profit, and return on investment (ROI)? Which instruments of economic evaluation are used in business and societal perspectives?
- **Period**: Which period is relevant for the decision-making, i.e. do we analyse the total cost of the entire lift-span of an equipment or only one period (e.g. year of purchase)?

8.2 Costs

The first question is answered by analysing the costs of the production of a commodity or service, i.e. $\sum_{i=1}^{n} c_i * y_i$. *Cost* is a financial expression of the consumption of resources [2, 3]. If a system has a certain level of resources and uses them to produce some services or commodity, the quantity and the value of the resources are reduced. Costs express this reduction of value in currency units, such as US$, €, or Shs (Kenyan currency). If, for instance, a manufacturer uses a piece of steel to produce the CT-scan, the value of this steel is part of his production cost. The consumption of this resource constitutes his cost. In the same way, the use of human labour and the wear and tear of equipment and buildings (depreciation) are costs.

We have to distinguish between payments, expenditure, and cost. A *payment* is the reduction of cash (cash on hand or bank account). However, this does not necessarily mean a loss of value of the enterprise. If we buy steel for the CT-scan production and put it on stock, we do not reduce the value of the enterprise. We pay a certain amount and get steel for exactly the same amount. Therefore, the net value of the enterprise is identical before and after this transaction. If we take the steel out of the stock and use it in the production process, the value of this steel is changed. We do not even know what the value of the CT-scan be. Maybe it cannot be sold and maybe the steel is spoilt during the production process. Therefore, the use of the steel generates cost, not the purchase.

Cost is only the reduction of the net worth of an enterprise if this reduction was necessary for the purpose of the enterprise. If, e.g. a business unit donates to the Red Cross, this reduces its net worth, but it is not necessary for the production process. Therefore, the term *expenditure* covers all reduction of net worth, whereas the term cost means only those expenditures that were necessary for the original purpose of the business unit. However, many authors use these terms interchangeable. More important is the fact that costs do not necessarily have to be connected with payments. For instance, the work of owner of an enterprise does not necessarily lead to a payment as in some forms of legal ownership he does not earn a salary. However, by working for his own enterprise he loses the opportunity to earn a salary

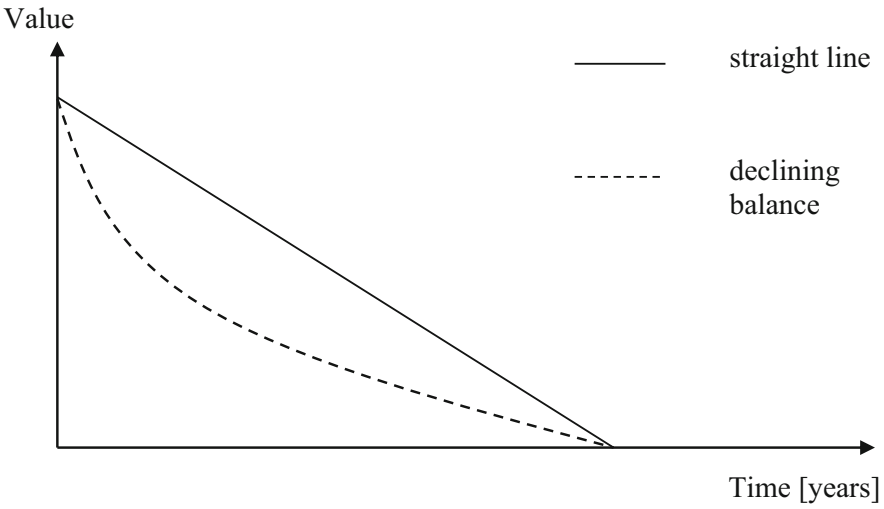

Fig. 8.2 Depreciation

elsewhere. Therefore, the value of a lost opportunity is named *opportunity cost* and has to be included in the total costs, although it is not connected with payments.

The most important resources to produce medical devices are personnel, raw materials, semi-produced goods, equipment, buildings, water, electricity, etc. Therefore, we have personnel costs, materials costs, equipment costs, costs of buildings, water, electricity, etc. We call these costs the *direct provider costs* because they occur directly in the production process. Salaries and wages, bills for materials, for water and electricity are, thus, costs. Buildings and equipment are established in 1 year for many other years to come. It would be completely inappropriate to charge all payments to the year of establishment. They are not consumed in this year, therefore only the wear and tear of the first year should be the cost of this year. Consequently, we only take a certain fraction of the original payment as the annual costs. This share is called *depreciation*.

Buildings and equipment do not lead to periodical payments. However, the wear and tear of these items has to be calculated. There are several possibilities. The easiest approach is to divide the original payment by the number of years that the item will be used. Figure 8.2 shows this as a straight line. It might also be possible to reduce the value of the item by a certain percentage every year, so that the annual depreciation is getting smaller every year (declining balance method). Finally, it is possible to include an interest rate for the investment. However, in most cases it is enough to calculate a linear depreciation.

The analysis has to distinguish *average cost* per service unit (such as cost per delivery) and *marginal cost* (such as additional cost for one additional delivery).

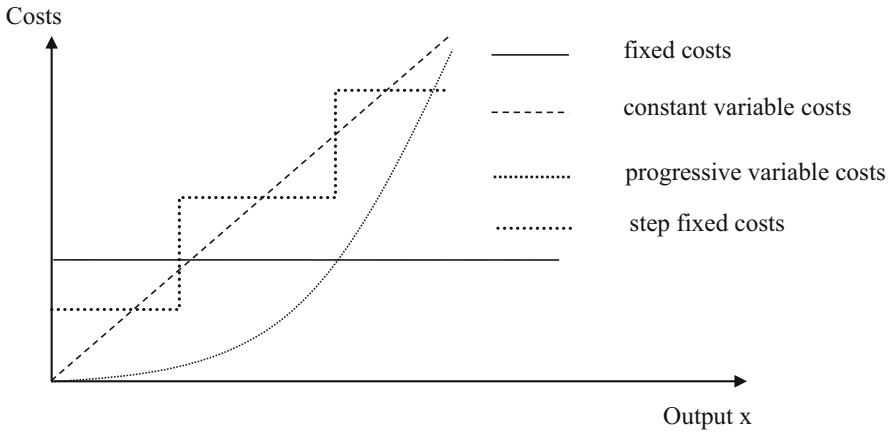

Fig. 8.3 Different cost development pattern

$$\overline{c} = \frac{C(x)}{x}$$
$$c' = \frac{\mathrm{d}C(x)}{\mathrm{d}x}$$

with

$\overline{c}$	unit cost
c'	marginal cost
$C(x)$	total cost
x	number of service units, i.e. bed days, deliveries, consultancies

The average cost is simply the quotient between total cost and the number of service units. For the calculation of the marginal cost, we have to distinguish between fixed and variable cost. *Fixed costs* do not vary with the volume of activity, whereas *variable costs* increase if we produce more goods. Normally, variable costs increase with volume, and the increase can be progressive, linear, or digressive. It has to be analysed, furthermore, whether fixed costs are indeed completely constant irrespective of the amount of services, or whether they are *step fixed*, i.e. they are stable until the activity reaches a certain level and then jump to a higher plateau to remain stable there as well. For instance, the costs for salaries of the sales force could be the same, whether the sales representative visits 10 or 20 clients per month. However, if the workload increases so much that one person cannot do the job alone, a second sales representative has to be hired and the costs jump by 100%. For any analysis, it will be important to know whether additional demand can be covered by the existing buildings, personnel, and equipment (Fig. 8.3).

Assuming a linear cost-function, we receive

$$\overline{c} = \frac{C(x)}{x} = \frac{C_\mathrm{f} + c_\mathrm{v} \cdot x}{x} = \frac{c_\mathrm{f}}{x} + c_\mathrm{v}$$
$$c' = \frac{\mathrm{d}C(x)}{\mathrm{d}x} = \frac{\mathrm{d}\{C_\mathrm{f} + c_\mathrm{v} \cdot x\}}{\mathrm{d}x} = c_\mathrm{v}$$

with

C_f	fixed cost
c'_v	constant variable cost

8.3 Outputs, Outcomes, and Impacts

The second aspect of any efficiency analysis are the outputs of a business unit, i.e. $\sum_{j=1}^{m} p_j * x_j$. If we analyse only the manufacturer of medical devices, the analysis of outputs is rather simple. He just has to add the sales in his different product lines to receive the turnover as total of outputs. However, in the long run this is insufficient. Medical devices make only sense if they have an impact on the health of the population by allowing better diagnostics or therapies. Thus, morbidity, mortality, days of sickness, reduced costs, increased productivity and in particular quality of life (QoL) are highly relevant for the analysis of outputs, i.e. manufacturers must also take a societal perspective to assess their outputs.

In order to understand this perspective, it is worthwhile to realize that diseases do not only have costs of diagnostics and therapy, but also much wider costs. As Fig. 8.4 indicates, the core provider costs are only one of many aspects of costs usually described as "Cost-of-Illness" (CoI) [5–18]. Households have direct and indirect costs. *Direct household costs* imply payments for transport to and from the health services, accommodation for the accompanying relatives, special building facilities for disabled patients (e.g. adapted bathroom), costs for diet and the re-education for both patients and relatives, for instance new training after a paralysis. Private households also have to bear direct payments for user fees and drugs that are an income of the providers.

Indirect household costs summarize all lost opportunities. During the time of illness, a patient and a relative taking care cannot work. Therefore, wage earners lose salaries as well as the economy production force. Sick parents do not have time to take care of their children so that their education will suffer either. Therefore, morbidity leads to indirect costs. The term "socio-economic costs" is used for the total of direct and indirect costs as both have to be shouldered by the society.

Direct and indirect household costs are so-called *tangible costs* because a monetary value can be attached to them. Pain, psychological pressure, reduced joy of life, and social prestige are reductions of the quality of life that do not have a natural monetary value. These *intangible costs* are sometimes evaluated as well and a monetary value is attached to them [19, 20].

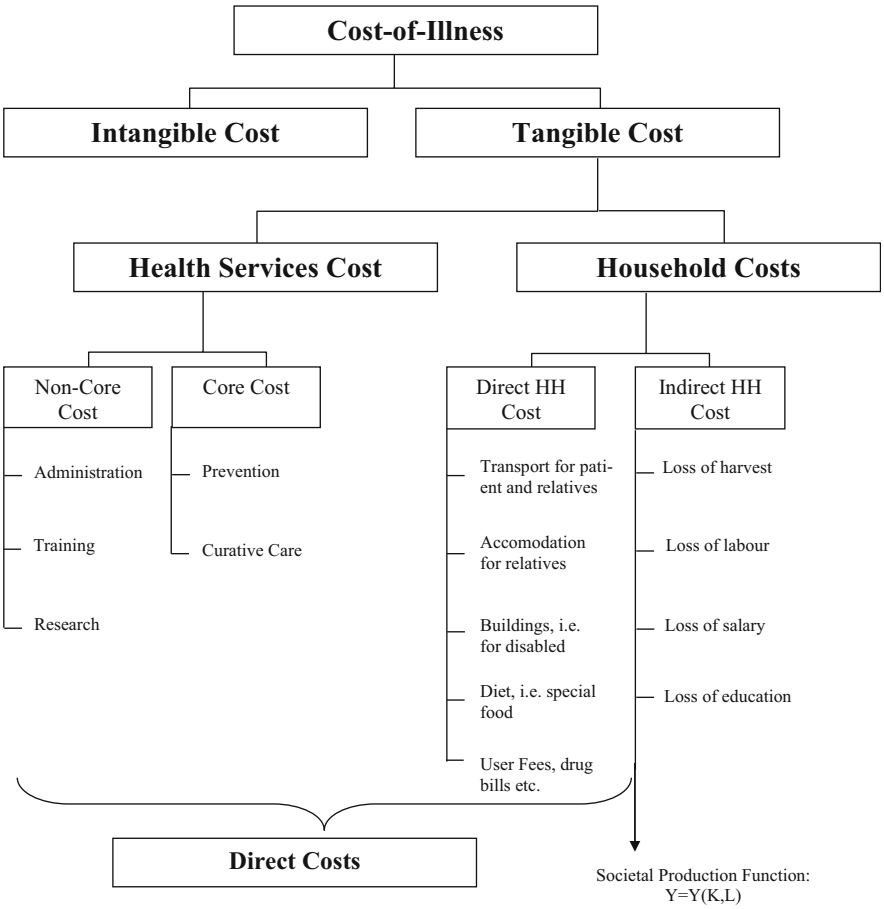

Fig. 8.4 Concept of cost-of-illness, based on ([4], #5563)

Consequently, outputs, outcomes, and impacts can be measured as a reduction of cost-of-illness. Only if an innovative medical device reduces the societal cost-of-illness the society will be willing to finance them. A narrow focus on the outputs of the manufacturer is often too narrow.

8.4 Performance

As stated above, we measure efficiency with the quotient

$$\frac{\sum_{j=1}^{m} p_j * x_j}{\sum_{i=1}^{n} c_i * y_i}$$

Measuring the costs (denominator) is rather simple, but finding a monetary expression for the numerator can be difficult. Some evaluation techniques try to do this. Others restrict the result to one dimension (e.g. life years gained); others artificially combine different results to one statistic according to certain rules. Thus, the degree of fusion differs from one economic evaluation technique to the other. The most important are:

- *Cost minimization*: The methodology [21, 22] assumes that the result of a health system or intervention is constant so that merely the costs have to be analysed. If we compare alternative services or interventions and if the result is equal to each other, the one with the lowest cost is the efficient service or intervention, the others are inefficient, i.e.

$$Z = \frac{\sum_{j=1}^{m} p_j * x_j}{\sum_{i=1}^{n} c_i * y_i} \rightarrow \text{Max!} \Leftrightarrow Z' = \sum_{i=1}^{n} c_i * y_i \rightarrow \text{Min!}$$

  Frequently the mentality of cost minimization has led administrators into the temptation to focus on costs only and to disregard the result of the healthcare activity, e.g. of an innovative technology. Consequently, future chances are neglected even if they were highly efficient because they would have required more resource input.
- *Result maximization*: Taken a given budget for a certain intervention, the efficient alternative is making the best out of these resources, i.e.

$$Z = \frac{\sum_{j=1}^{m} p_j * x_j}{\sum_{i=1}^{n} c_i * y_i} \rightarrow \text{Max!} \Leftrightarrow Z' = \sum_{j=1}^{m} p_j * x_j \rightarrow \text{Max!}$$

  This methodology [21] can be applied if the budget is without competition to other allocations of funds. In reality, healthcare or a particular programme or service is always only one possible allocation of funds, i.e. the amount earmarked for this purpose will vary so that this methodology is restricted to few applications within very limited fields.
- *Cost-benefit analysis*: A cost-benefit analysis [22] expresses inputs and results in monetary terms, i.e. not only the costs, but also the incidence, prevalence, life years, death cases, and quality of life are expressed in currency units, i.e.

$$Z = \frac{\sum_{j=1}^{m} p_j * x_j}{\sum_{i=1}^{n} c_i * y_i} \rightarrow \text{Max!} \Leftrightarrow \Pi = \sum_{j=1}^{m} p_j * x_j - \sum_{i=1}^{n} c_i * y_i \rightarrow \text{Max!}$$

  The disadvantages of a cost-benefit analysis are obvious: It is very difficult to express human life in monetary terms, and all constructions to do so will bear ethical problems. However, the cost-benefit analysis has strong advantages if we want to compare alternative allocations of funds beyond sector borders. For

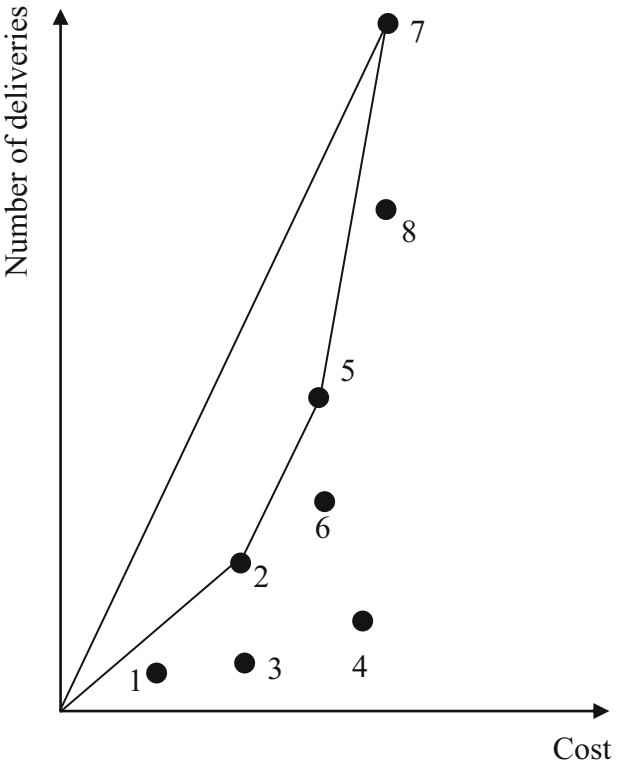

Fig. 8.5 Cost-effectiveness analysis, based on [1]

instance, an investment into education and into healthcare can only be compared if we find a common dimension of results.

Money is a weak common dimension, but maybe the only possible one.

- *Utility analysis*: The utility analysis treats inputs and results as one dimension and expresses all quantities in a single utility score [23, 24]. Therefore, costs for resources are not expressed in financial terms but in an ordinal scale (highest, high, lower ...). Seeing the high importance of costs and budgets in the healthcare sector, this approach is not satisfactory.
- *Cost-effectiveness analysis*: The cost-benefit analysis fuses input and result into one statistic (e.g. surplus). The cost-effectiveness analysis [25, 26] expresses the inputs in monetary terms, but the results are measured in physical units, e.g. number of children immunized. Input and result represent two dimensions, so that this analysis frequently does not produce a single alternative, but a set of alternatives forming an efficiency frontier. Figure 8.5 demonstrates an example of eight health centres in a district offering delivery services. The total costs of this service per health centre are compared with the number of deliveries. It is obvious that health centre seven has the lowest cost per delivery: it is efficient. However, if

we assume economies of scale, it might be useful to include also unit 2 and 5 as efficient, so that units 2, 5, and 7 form the efficiency frontier.

The units on the frontier are efficient and form the set of benchmarks for the other units, i.e. unit 3 should concentrate on the performance of unit 2. If we assume constant elasticity of scale, only unit 7 is efficient, but for the small unit 3 it is not helpful to attempt at learning from this big health centre.

- *Cost-utility analysis*: This analysis allows that the result is not a single physical unit but an indicator that combines several statistics. For instance, quality of life and life years are combined in the Disability Adjusted Life Year (DALY). The combination will always be artificial and subject to discussion.

Most manufacturers of medical devices and a major share of healthcare facilities are for-profit enterprises that can derive their goal function directly from the original efficiency quotient, i.e.

$$Z = \frac{\sum_{j=1}^{m} p_j * x_j}{\sum_{i=1}^{n} c_i * y_i} \rightarrow \text{Max!} \Leftrightarrow \Pi = \sum_{j=1}^{m} p_j * x_j - \sum_{i=1}^{n} c_i * y_i \rightarrow \text{Max!}$$

The term $\prod$ is the profit calculated as the difference of total revenue and total cost. In other words, any for-profit enterprise that maximizes its profit will also maximize its efficiency. Profit is a signal of efficiency. These enterprises will adopt a new medical device as innovation if it allows them to increase their profit—and this is consistent and ethically sound because it will allow them to use the resources most efficiently.

However, profit is usually insufficient to assess the advantage of an investment, project, or enterprise. One million € of profit is very high for a private practitioner, but it is very little for an international company. Thus, we have to relate the profit to the capital invested. The respective quotient is called "return on investment" (ROI). The following formula defines ROI demonstrating its components of profit (numerator) and capital with its component's equity (capital from owners of the enterprise) and liability (loans from non-owners). Consequently, an investment (such as the development of a new medical device) is seen as profitable if the ROI is greater than the market interest rate, i.e. the rate which is received if the funds are not invested in the development of the medical device but invested in the capital market.

$$\text{ROI} = \frac{\Pi}{K} = \frac{\sum_{j=1}^{m} p_j * x_j - \sum_{i=1}^{n} c_i * y_i}{E + L} \rightarrow \text{Max!}$$

Consequently, we can state that the costs of healthcare services, projects, and medical devices are highly relevant for any type of economic analysis. Costs are always the starting point and knowing the costs is the prerequisite for any other assessment.

8.5 Period

Usually, a major share of the resources is consumed before any sales are made. Cost for development and marketing of a new medical device can be as high as the production costs during the next years. Consequently, the profitability of a product has to take several periods into consideration. During the first periods, costs will be higher than revenues, later on this will most likely change. If no interest is accounted for, we can just add all costs and revenues and compare them. If interest has to be paid for capital, all costs and revenues have to be discounted so that they can be compared. This is usually done with the formula

$$PV = \sum_{t=1}^{l} (R_t - C_t)(1 + r/100)^{-t}$$

with

CV	Present value
R_t	Revenues of period t
C_t	Cost of period t
r	Rate of interest
l	Lengths of life of investment

It is necessary to assess all costs and revenues through the lengths of life of an investment. In the case of a medical equipment producer, this covers developments costs, marketing costs, production costs, disposal costs, etc. For the user of a medical equipment it covers the total cost of acquisition and operation, costs related to replacement or upgrades at the end of the life cycle as well as indirect costs such as training with the new equipment. The wider concept with a life-long perspective is called "total cost of ownership" (TCO).

Conclusion

Inventing, developing, producing, and marketing of medical devices is not different from any other commodity. Even if producers are completely convinced of the superiority of their product, they must also convince customers to buy these products and pay a sufficiently high price for it. According to experience, entrepreneurs and co-workers of medical device factories are quite committed to their products and they see a chance to contribute to the well-being of the human population with them. However, business does not work by good intentions or beliefs, but by sales. All thinking must start with the needs of people. At the end, the sick will decide whether they want this product or not—and whether they are willing to pay for it.

In the reality of modern societies with Health Insurances and Government subsidy, the reality is more complex as many Government bodies (e.g. National Institute for Health and Care Excellence, NICE, UK; Gemeinsamer Bundesausschuss, GBA, FRG) and insurances decide on the portfolio of diagnostic

and therapeutic devices. At the same time, medical practitioners have a double role as provider of healthcare services and consultant to the patient indicating what service he requires. Thus, healthcare markets are more complex than traditional commodity markets. However, at the end it is the patient who will be operated on, is x-rayed or receives an implant. And eventually it is the tax payer who decides whether the product is worthwhile its costs on the individual and in particular on the societal level.

Consequently, a thorough analysis of costs and benefits for all stakeholders as well as throughout the entire process states is a crucial prerequisite of successful medical device production. Even the very best product idea without proper management and without precise costing will never benefit anybody.

Take Home Message

- The production and utilization of medical devices induce costs.
- Costs have to be recovered by revenues to be sustainable.
- Customers are only willing to pay sufficiently for a product if it satisfies their needs, i.e. the output, outcome, and impact must be worthwhile.
- Knowing or predicting costs and revenues is essential for the success of medical device production and utilization.
- Medical devices produce outcomes and impacts which are highly relevant for the individual and the society. Proper management and cost control are needed in order to ensure their benefits.

References

1. Fleßa S (2018) Systemisches Krankenhausmanagement. De Gruyter Studium
2. Wöhe G, Döring U (2005) Einführung in die Allgemeine Betriebswirtschaftslehre. 22., neubearb. Aufl. ed. Vahlens Handbücher der Wirtschafts- und Sozialwissenschaften. Vahlen, München
3. Lucey T (2002) Costing. Thompson Learning, London
4. Fleßa S, Greiner W (2020) Grundlagen der Gesundheitsökonomie. Springer, Berlin
5. Neubauer S et al (2006) Mortality, morbidity and costs attributable to smoking in Germany: update and a 10-year comparison. Tob Control 15(6):464–471
6. Keith R, Shackleton P (2006) Paying with their lives: the cost of illness for children in Africa. Save the Children Fund, London
7. Welte R, König HH, Leidl R (2000) The costs of health damage and productivity losses attributabel to cigarette smoking in Germany. Eur J Public Health 10:31–38
8. Leidl R (1999) Deutsches Institut für Medizinische Dokumentation und Information,Deutschland. Bundesministerium für Gesundheit *Ansätze und Methoden der ökonomischen Evaluation: eine internationale Perspektive*. 1. Aufl ed. Health technology assessment. Nomos-Verl.-Ges, Baden-Baden
9. Henke K-D, Martin K, Behrens C (1997) Direkte und indirekte Kosten von Krankheiten in der Bundesrepublik Deutschland 1980 und 1990. Diskussionspapier/Wirtschaftswissenschaftliche Dokumentation, Technische Universität Berlin, Berlin
10. Single E et al (1998) The economic costs of alcohol, tobacco and illicit drugs in Canada, 1992. Addiction 93(7):991–1006

11. Xie X et al (1998) The economic costs of alcohol abuse in Ontario. Pharmacol Res 37(3):241–249
12. Single E et al (1999) Morbidity and mortality attributable to alcohol, tobacco, and illicit drug use in Canada. Am J Public Health 89(3):385–390
13. Xie X, Mann RE, Smart RG (2000) The direct and indirect relationships between alcohol prevention measures and alcoholic liver cirrhosis mortality. J Stud Alcohol 61(4):499–506
14. Hodgson TA, Meiners M (1979) Guidelines for cost of illnesss studies in the Public Health Services, studies Tfocoi, Editor. US Public Health Services
15. Caro JJ et al (2005) Pertussis immunization of adolescents in the United States: an economic evaluation. Pediatr Infect Dis J 24(5 Suppl):S75–S82
16. Dong H et al (2005) Inequality in willingness-to-pay for community-based health insurance. Health Policy 72(2):149–156
17. van Roijen L et al (1995) Indirect costs of disease; an international comparison. Health Policy 33(1):15–29
18. Carabin H et al (2003) The cost of measles in industrialised countries. Vaccine 21 (27–30):4167–4177
19. Breidert C (2006) Estimation of willingness-to-pay: theory, measurement, application. 1. Aufl. ed. Gabler Edition Wissenschaft. Dt. Univ.-Verl, Wiesbaden
20. Gertler P, van dGJ (1990) The willingness to pay for medical care: evidence from two developing countries. Johns Hopkins University Press, Baltimore, MD, p 133
21. Evans DB, Hurley SF (1995) The application of economic evaluation techniques in the health sector: the state of the art. J Int Dev 7(3):503–524
22. Drummond MF (2005) Methods for the economic evaluation of health care programmes, 3rd edn. Oxford Medical Publications/Oxford Univ. Press, Oxford
23. Murray CJL (2003) Health systems performance assessment: debates, methods and empiricism. World Health Organization, Geneva
24. Murray C et al (2002) Summary measures of population health: concepts, ethics, measurement and applications. World Health Organization, Geneva
25. Muennig P (2002) Designing and conducting cost-effectiveness analysis in medicine and health care. Jossey-Bass Inc., San Francisco
26. Tan-Torres ET (2003) World Health Organization making choices in health: WHO guide to cost-effectiveness analysis. World Health Organization, Geneva

Chapter 9
Assessment of Medical Technologies: Methods and Challenges

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Abstract The present situation of the healthcare systems worldwide strongly calls for a change in the care delivery paradigm and requires to focus more on the long-term outcomes and on what is of real value for patients and the community. This approach can be summarized with the value-based healthcare concept, which can be greatly sustained by the technology innovation. The chapter focuses on the assessment of medical technologies, with special attention to medical devices, and on different methods and problems connected with this evaluation. Special emphasis is given to the different methods (e.g. health technology assessment, cost-utility analyses, and others), and to investment/divestment decisions. The issues of the social return of the investment in healthcare and of the legitimacy of the decisions taken are also considered.

The discussion is then completed with the presentation of the emerging topics about the assessment of medical technologies.

Introduction

For the creation of the best care value for patients and community, the assessment of the medical technologies and innovation, with special attention to medical devices, is needed.

The analysis has to start with the concept of value in healthcare followed by the examination of the different methods for technology evaluation and the definition of investment strategy.

The innovation in hospitals should further not be neglected.

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9.1 The Concept of "Value" in Healthcare

The recent pandemic has made it clear to citizens, hospital professionals, and policymakers that the current paradigms of healthcare delivery must be reloaded. Among the many lessons learnt, one of the most relevant issue is about the role that "innovation" should play in order to rethink and improve healthcare delivery. The focus has shifted from short-term outputs over medium- to long-term outcomes [1]. What matters is the actual capability of healthcare providers (e.g. family doctors, acute and rehabilitation hospitals) to impact positively and significantly the quality of life of citizens and the competitiveness of the served society [2].

This new approach to healthcare delivery is widely known as "Value-Based Healthcare" (VBH). The concept of "value" stems from the original formulation by Porter and Teisberg [3] and is defined as the ratio between the health outcomes that matter to patients and the cost of delivering that outcome. This concept is still under discussion, but there is a growing consensus that the shift from outputs to outcomes obliges healthcare delivery to meet four requirements: participation, personalization, prevention, and prediction [4]. Even if the in-depth discussion of these requirements is beyond the scope of this chapter, a few examples might show their relevance and urgency. First, citizens are claiming for a more active role in the management of their health/disease, because of their progressive empowerment in terms of health literacy, revisiting the traditional scope of the patient–physician alliance. Second, precision medicine has gone far beyond the borders of DNA-based diagnostics to also cover service delivery, acknowledging that socio-demographic factors might affect citizens' experience with the delivery of care and their adherence to therapy/lifestyle. Third, as it happened in other industries, healthcare should deliver care to citizens when they are still healthy to reduce, and possibly avoid—or at least to postpone—the emergence of (chronic) diseases. Fourth, decision-makers are more and more provided with accurate predictions about what might happen and what should be the most effective interventions due to the increased availability of data and the development of machine-learning algorithms. Healthcare providers are needed to explore either new processes or practices to meet these requirements, matching different organizational arrangements and technological configurations [5]. These changes must ground on innovations. Among the different sources of innovation, the seamless development of innovative medical technologies is one of the most relevant ones and the assessment of their potential impact on value generation is the focus of this chapter. Figure 9.1 offers a synthetic view of the linkage between value-based healthcare and innovative medical technologies.

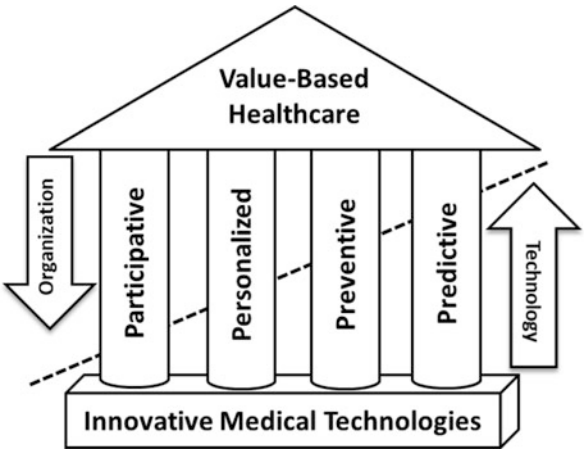

Fig. 9.1 Value-based healthcare and its "pillars"

9.1.1 Value-based Healthcare and Technology Assessment

The increased pace of technological development in healthcare, combined with shrinking financial resources available to adopt them, obliges decision-makers to select, among the most promising innovations, only those that can demonstrate the best value-for-money—i.e. those innovations that prove to generate enough benefits compared to their costs [6]. In this view, how to support decision-making at different levels (national/regional/local/hospital/department/professional) has risen as a priority on the agenda of practitioners and scholars of biomedical engineering, health economics, and medicine. In the last years, the worldwide debate on decision-making concerning the adoption of novel medical technology has grown around the concept of legitimacy. Decision-making must be legitimate. This is particularly relevant for all national healthcare systems whose activities and investments in novel medical technology are based on citizens' taxes.

Legitimacy can be defined as "*a generalized perception or assumption that the actions of an entity are desirable, proper, or appropriate within some socially constructed system of norms, values, beliefs, and definitions*" [7]. This definition clarifies that what is legitimate is socially constructed and might differ in different social groups (e.g. in different healthcare systems). Legitimate decision-making should consider the point-of-view of different groups of stakeholders, such as patients, caregivers, patient advocacy groups, hospital professionals and managers, suppliers, payers, and policymakers. Past research [8] identified four requirements that should ground legitimate decision-making in healthcare. They are (1) rationality, (2) fairness, (3) efficiency, and (4) evidence, as shown in Fig. 9.2.

Figure 9.3 synthesizes the main implications related to the four requirements. Legitimate decision-making should ground on rational methods and processes. In particular, the assessment of novel medical technologies should crystallize the most relevant criteria that can help to gather the most comprehensive understanding of the implications due to their adoption. These criteria should cover different domains,

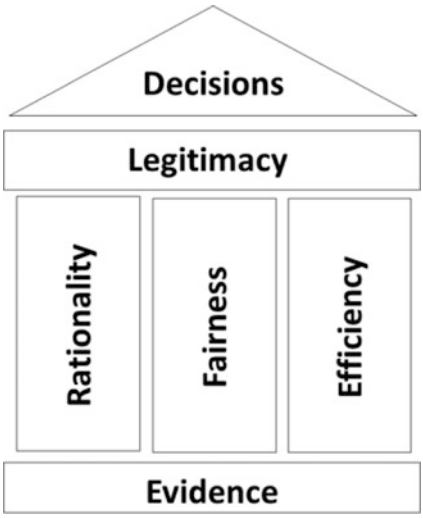

Fig. 9.2 Requirements of legitimate decision-making in healthcare

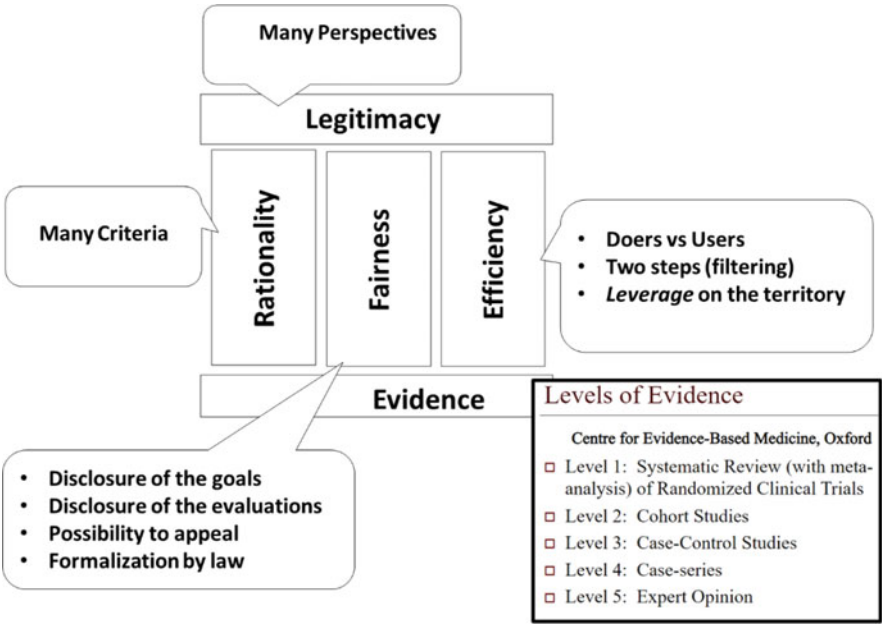

Fig. 9.3 Criteria for legitimate decision-making in healthcare

such as effectiveness, safety, organizational impacts, and efficiency. Legitimate decision-making should be fair, i.e. no group of stakeholders (or beneficiaries) should be privileged or disadvantaged. Past studies identified four conditions for guaranteeing fairness. First, goals of assessment and decision-making should be disclosed. Second, the methods and results of evaluations should be also disclosed.

Third, all groups of stakeholders should be in the condition to appeal to evaluations if they think either that some pieces of evidence have been overlooked or some parts of the evaluation should be revised because being incorrect. Fourth, all these elements should be formalized through laws. Legitimate decision-making should be efficient. The pace of technological development in healthcare is very high and, even if from a theoretical perspective all innovations should be assessed to prove their value-for-money, from a practical perspective this is not feasible. In this view, three arrangements might be implemented. First, users rather than doers should oversee the assessment of novel medical technologies. This means that they should try the best they could to reuse the assessment reports produced by other entities—through collaborative networks—and produce reports only for those innovations that have not been assessed yet by others.

Second, the available resources for assessment, in terms of time and money, should be focused on a subset of innovations through the crystallization of filtering mechanisms, thus designing a two-stage approach—as done, for example, for the proposals of funding that are submitted to the European Commission. Third, entities that oversee technology assessment should try to leverage the competencies and resources that are available on the territory, involving universities, research centres, scientific associations, hospitals, patient advocacy groups, etc. Finally, these requirements (i.e. rationality, fairness, efficiency) should ground on evidence, as recommended by evidence-based medicine. Dealing with innovations, evaluators will face situations characterized by different levels of evidence, ranging from high levels (e.g. meta-analyses, randomized clinical trials) for more mature medical technologies to low levels (e.g. expert opinions, case series) for emerging ones. This consideration paves the way for discussing the difference between Health Technology Assessment (HTA) and Horizon Scanning (HS). Even if the large audience is more familiar with the concept of HTA when debating about the assessment of novel medical technologies, in the next section the distinction between HTA and HS will be addressed.

9.1.2 Health Technology Assessment

Health Technology Assessment (HTA) has been defined as a form of policy research that examines the short- and long-term consequences (e.g. societal, economic, ethical, legal) of the application of medical technology [9]. It aims at providing decision-makers with the information they need. They may not be able to judge the benefits or consequences of medical technology within a strictly technical context. They must consider the social, economic, and legal implications of any course of action. However, very frequently, the comprehensive information needed by decision-makers is either not available or not in the right form. This supports further the still ongoing debate about what should be the information domains considered by HTA reports, addressing rationality for legitimacy.

Before discussing the proposals that have been developed within the Cost-Utility Analysis (CUA) and the Multi-Criteria Decision Analysis (MCDA) in terms of relevant informative domains, it is worth to clarify the distinction between assessment and decision-making. They are different domains that refer to distinct responsibilities. The separation between those who assess and those who decide upon is connected to legitimacy. Regulators must clarify policy needs and translate them in research questions that researchers from different disciplines can investigate through the design of coherent research projects aimed at gathering robust results. HTA offers the methods to answer the research questions agreed between regulators and researchers. The responsibility of researchers ends once research questions have been answered. Regulators are not involved in the production of results, but their role is to decide upon them—either positively or negatively. Regulators can reject legitimately researchers' results. This might happen either because results overlook relevant pieces of information or because methods that have been applied are not agreed. Therefore, it is necessary a wide agreement—better at the international level—of the language, the methods and reporting that should be employed by those running HTA exercises. In this view, the efforts made in the last years by the INAHTA—the International Network of Agencies for Health Technology Assessment—are worth to mention, with particular attention to the development of (1) an agreed glossary of HTA-related terms with their meaning, (2) a coherent portfolio of methods and tools for the design and carry-out of HTA exercises; (3) a checklist to evaluate the robustness of HTA reports; and (4) a database of past HTA reports facilitating the reuse of the already available assessments.

A similar effort has been made by the EUnetHTA (European network for Health Technology Assessment) European collaboration. This initiative, funded by the European Commission, established a network for HTA across Europe to help the production of reliable, timely, transparent, and transferable information about medical technology. In particular, the network aims at an efficient resource use for HTA (promoting the reuse of previous reports), the sharing of expert knowledge about HTA, and the crystallization of a coherent set of good practices for HTA. In this view, one of the most relevant contributions has been the development of the Core Model reference framework for HTA [10, 11]. Nine domains have been identified as the most relevant for supporting decision-making (Table 9.1). They are:

1. Health problem and current use of technology
2. Description and technical characteristics of the technology
3. Safety
4. Clinical Effectiveness
5. Cost and economic evaluation
6. Ethical analysis
7. Organizational aspects
8. Patient and social aspects
9. Legal aspects

According to EUnetHTA, two different HTA reports can be delivered. On the one hand, decision-makers might be interested in a comprehensive assessment—also

Table 9.1 HTA domains according to the EUnetHTA collaboration

HTA core model domains			
Comprehensive/ Full HTA	*Rapid Relative Effectiveness Assessment (REA)*	Domains whose analysis can be valid for different countries and facilitate the reuse of the HTA report	Health problem and current use of technology
			Description and technical characteristics
			Safety
			Clinical Effectiveness
	Country-specific Appraisal	Domains whose analysis might differ country by country because of the peculiar characteristics	Cost and economic effectiveness
			Ethical analysis
			Organizational aspects
			Patient and social aspects
			Legal Aspects

known as "full HTA report"—that covers all nine criteria. This might be the case for more mature medical technologies, whose evidence is more consistent and broader. On the other hand, decision-makers might be interested in a less comprehensive, more focused assessment. This is the case for a Rapid Relative Effectiveness Assessment (REA) that covers just the first four criteria. This might be the case for emerging medical technologies, whose evidence is more limited and still focused on clinical effectiveness and safety. Interestingly, this distinction is useful also to discuss the potential reuse of HTA reports.

The distinction between "mature" and "novel" medical technologies is salient for their assessment because of different levels of evidence. HTA requires significant bodies of high-quality evidence to support decision-making. Because of that, HTA is usually associated with mature technologies and it is mainly used to manage the diffusion or the disposal of medical technologies that are already in use somewhere. Where the medical technology under assessment is emerging or innovative—meaning that the technology is at the beginning of its diffusion in the healthcare system and that the available evidence is still limited and of lower quality—the assessment refers more to Horizon Scanning (HS) than to HTA [12]. Even if the domains and criteria might be shared among HTA and HS, their difference grounds on the level of evidence that informs assessment reports and the strength of the recommendations that will be submitted to decision-makers.

From a practical perspective, HS reports are of paramount relevance. Where decision-makers are enabled to know in advance that some promising medical technologies will access soon the market and will be available for the clinical practice, they can act to prepare the field to enable and facilitate their fast

diffusion—e.g. developing the required legal framework, providing healthcare professionals with the required competencies.

9.1.3 Economic Assessment of Technology in Healthcare

The economic assessment aims at providing decision-makers with useful, complete, robust evidence about which healthcare strategy—or medical technology—should be preferred among the available alternatives (known as comparators) [6]. The alternatives are benchmarked in terms of consequences and costs (Fig. 9.4). Among the "consequences", the assessment must consider all benefits that derive from the adoption of a specific healthcare strategy/medical technology in terms of any improvement of patients' health or well-being. This refers to the concept of "effectiveness" of a healthcare strategy/medical technology. Among the "costs", the assessment must consider all resources consumed by the adoption of a specific healthcare strategy/medical technology. These resources might be provided by (1) the healthcare system (e.g. from local health agencies, hospitals, nursing homes), (2) the patient or her/his family (e.g. in terms of patient's time, caregivers' time, travel costs); (3) other sectors (e.g. from non-profit organizations, social enterprises). When resources from all sources are included, the economic assessment takes a "societal perspective". Vice versa, when only resources from the healthcare system are considered, the economic assessment takes a "healthcare system perspective". The choice between the two perspectives is related strictly to the specific healthcare strategy/medical technology under assessment. For instance, in the case of mental care services, almost half of the costs come from the patients (and their families) and other sectors. In such a context, a societal perspective should be preferred to provide decision-makers with a more comprehensive understanding of the benefits and costs associated with different alternatives (comparators).

The economic assessment of the different alternatives can be conducted with four main techniques [13] that are pointed out in Fig. 9.5. The distinction among them

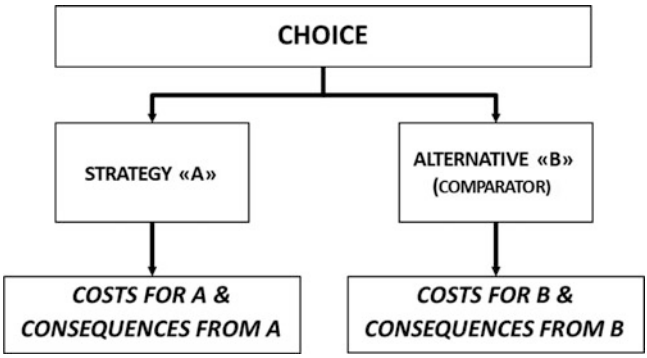

Fig. 9.4 Setting decision-making about technologies in healthcare

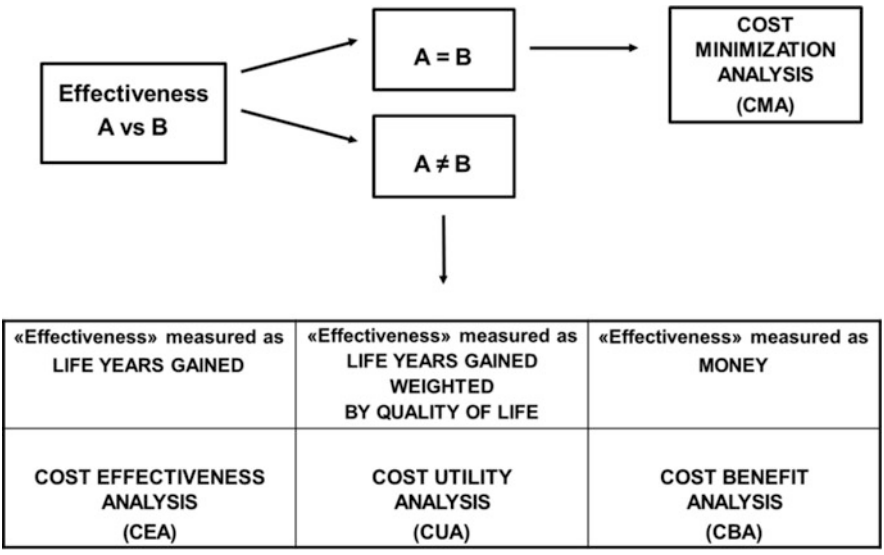

Fig. 9.5 Setting decision-making about technologies in healthcare

relies on how they analyse consequences (effectiveness). If the different alternatives offer similar consequences, the economic assessment compares them against costs, preferring the alternative that minimizes the consumption of resources—namely Cost Minimization Analysis (CMA). This analysis is almost rare because the typical situation is that novel medical technologies claim superior benefits with respect to comparators. An example refers to telemedicine, where economic studies assume that telemedicine offers similar benefits in comparison to face-to-face clinical practice and, in this view, assess potential cost savings (e.g. [14]). Where the alternatives offer different consequences, they can be measured in different ways. The most widely used approach is to measure benefits with primary endpoints—e.g. reduction in mortality or number of life years gained. In this case, the economic assessment is a Cost-Effectiveness Analysis (CEA). Another approach is to measure consequences such as the combination of primary endpoints (life years gained) with an outcome measure such as Quality of Life (QoL), introducing Quality-Adjusted Life Years (QALYs) as a synthetic indicator that captures both variations (quality and quantity). This economic assessment—known as Cost-Utility Analysis (CUA)—should be preferred in the case of diseases or events that, despite they do not affect patients' mortality, reduce, with different levels of severity, their quality of life (e.g. limb amputation, chronic degenerative diseases, kidney failure, coma state). Finally, consequences can be measured in terms of saved costs or value generated, using currency as a unit of measure. This allows a direct comparison—in monetary terms—between benefits and costs (Cost-Benefit Analysis—CBA). The valorization of benefits can be done using different approaches such as the measurement of patients' Willingness-To-Pay (WTP) or revealed preferences.

Table 9.2 Characteristics of the four techniques for economic assessment

Analysis	Costs (measured as . . .)	Consequences (measured as . . .)	Level of use	Strengths	Weaknesses
CMA	Money	There is no measure because they are similar	Low	Consequences re not to be measured	It works only for alternatives with similar consequences
CEA	Money	Disease-related measure	High	Strict relation with the disease	It works only for alternatives in the same clinical domain
CUA	Money	QALYs (Quality-Adjusted Life Years)	Medium	It works for alternatives with different consequences	QALYs receive critics and their measurement is not easy
CBA	Money	Money	Low	It works for alternatives with different consequences	Measuring consequences as "money" is not easy

Table 9.2 offers a synthetic view of the characteristics of the four methods, also in terms of strengths and weaknesses. Among the methods, scholars of health economics recommend CUA as a reference technique for the economic assessment of different healthcare strategies/medical technologies.

In this view, the next section will detail briefly CUA.

9.1.4 Cost-Utility Analysis

Cost-Utility Analysis (CUA) measures the consequences of alternative healthcare strategies/medical technologies by combining quantity and quality of life (QoL) into Quality-Adjusted Life Years (QALYs) [6, 13]. QALYs—that can be computed as the product of life years times the achieved QoL—measure the utility (i.e. the value) generated by a specific healthcare strategy/medical technology. From a theoretical perspective, QoL is a value that goes from 0 to 1, where "1" indicates a situation where the patient has full QoL (this state is typically associated to perfect health) and "0" indicates a situation where the patient has a nil QoL (this state is typically associated to death). Figure 9.6 shows the comparison between two alternatives, A vs B, in terms of the expected length of life before death (horizontal axis) and the expected quality of life (vertical axis).

The incremental benefits generated by the adoption of strategy/technology B (with respect to A) can be measured as the difference between the two areas below the two curves of QoL.

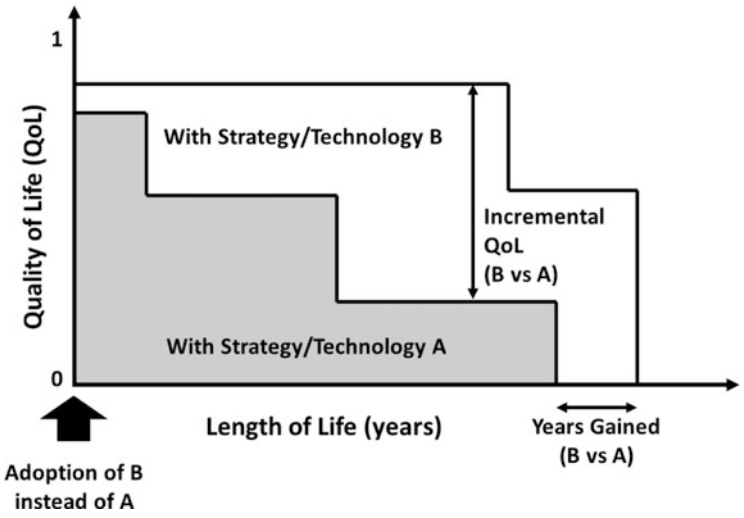

Fig. 9.6 Quality-adjusted life years as a synthetic index

The advantage of CUA compared to CEA is that, while CEA measures consequences just as years gained (i.e. the difference that is shown on the horizontal axis), CUA weights the length of life by the expected QoL, thus providing decision-makers with a more comprehensive understanding of the utility (i.e. the value) generated by different alternatives. This is particularly relevant in those cases where diseases or traumatic events do not affect patients' mortality, such as limb amputation, but they affect QoL [15].

The measurement of QoL is the most critical phase in a CUA. While clinical studies offer evidence about the expected length of life because of alternative healthcare strategies/medical technologies, evidence about the related QoL is less available and must be collected and measured in dedicated economic studies. There are different methods to measure QoL that ground on different theoretical assumptions. On the one hand, there are methods—e.g. the Visual Analogue Scale or Rating Scale, the Standard Gamble, and the Time Trade-Off—that measure individual preferences. These methods share the assumption that QoL is definitively subjective and patients who share the same health situation might perceive a different QoL. On the other hand, there are methods—e.g. the EQ-5D-3L—that measure the health status because they postulate that QoL is determined mainly by the health status of patients and that, in this view, patients who share similar health status perceive similar QoL.

In the followings, the most established methods are described briefly.

The Visual Analogue Scale (VAS) is the simplest and most frequently employed method. It consists of a straight horizontal (or vertical) line of fixed length, usually 100 mm, orientated from the left (worst QoL = 0) to the right (best QoL = 100). The patient indicates her/his perceived QoL on this scale. Collecting the

socio-demographic characteristics of the patient as well as her/his preferences, the researcher, through a regression analysis, can identify those factors that explain QoL.

Concerning the Standard Gamble, the researcher proposes to the patient a hypothetical situation where an intervention is available that might restore her/his perfect health but with a probability $(1 - x)$ to die. The patient is asked to choose between two alternatives (gamble): (a) refuse that intervention and remain in the current condition of imperfect health; (b) accept the intervention (probability of success equal to x). The probability x must be varied until the patient is indifferent between the two alternatives. When the patient cannot decide between them, this means that the utility of the two alternatives is equal (i.e. length of life times QoL). From this equality, it is possible to determine that the QoL of the current health status is equal to x.

Similarly, to the Standard Gamble, the usage of the Time Trade-Off approach requires the researcher to propose to the patient a hypothetical situation where an intervention is available that might restore her/his perfect health but with the side effect to reduce her/his life expectancy from "t" to x. The patient is asked to choose between two alternatives: (a) refuse that intervention and live in a condition of less than perfect health for "t" years; (b) accept the intervention and live x years in perfect health (being x lower than "t"). Time x has to be varied until the patient is indifferent between the two alternatives. When the patient cannot decide between them, this means that the utility (i.e. length of life per QoL) of the two alternatives is equal. From this equality, it is possible to determine that the QoL of the current health status is equal to x/t.

The Euro Quality of Life—5 Dimensions—3 Levels (EQ-5D-3L) approach postulates that QoL is strictly related to the patient's health status and that patients with a similar health status perceive a similar QoL. In this view, QoL is determined by the identification of the current health status of the patient. The health status is evaluated against five dimensions: (1) mobility; (2) self-care; (3) usual activities; (4) pain and discomfort; (5) anxiety and depression. For each dimension, the patient has to report her current status against three levels: (1) no problems; (2) some problems; (3) extreme problems. This allows the researcher to characterize the current health status of the patient with a numerical code. For instance, the sequence 21123 indicates a patient who faces some problems to walk, has no problems with self-care, has no problems with doing usual activities, has a moderate pain/discomfort, and who is extremely anxious/depressed. QoL of the current health status is determined by subtracting to 1 (perfect health) specific coefficients associated with levels 2 or 3 (i.e. situations where the patient is not in perfect health).

Once QALYs have been determined—by calculating QoL with one of the methods described above—they are compared to the consumption of resources—accordingly to the societal or the healthcare system perspective. The comparison between consequences (QALYs) and costs of two alternative healthcare strategies/medical technologies (e.g. A vs B) is carried out through the Incremental Cost-Utility Ratio (ICUR). The ICUR is calculated as the ratio between the incremental costs (costs(B) minus costs(A)) and incremental utility (utility(A) minus utility(B)). In this view, the ICUR means the incremental cost that the healthcare system (or the

society as a whole) must sustain to provide the patient with an additional year in perfect health. This value is compared to a threshold defined by policymakers. The most representative threshold in Europe is the one defined by the National Institute of Clinical Excellence (NICE) equal to 58,600 €/QALY. This implies that only those healthcare strategies/medical technologies whose ICUR against the current practice is lower than 58,600 €/QALY will be considered eligible for reimbursement. The ICUR calculation should be performed for subgroups of patients—e.g. see Cutti et al. [15]—to identify which ones might benefit the most from the adoption of the healthcare strategy/medical technology under assessment and help decision-makers to prioritize the usage of limited financial resources. Similar lines of reasoning can be developed in the case of different healthcare strategies/medical technologies. By comparing them against the additional resources needed to generate one additional year in perfect health, policymakers can rank different healthcare strategies/medical technologies from the most efficient to the most expensive (i.e. accordingly to higher values of ICUR) and develop League Tables [16] to support the prioritization of resource allocation.

9.1.5 Multi-criteria Decision Analysis

In the last years, doubts have arisen about the capability of Cost-Utility Analysis (CUA) to capture the multifaceted consequences generated by alternative healthcare strategies/medical technologies. The progressive establishment of the main principles of Health Technology Assessment (HTA)—rationality, in particular—made clear that decision-makers need evidence about the short- and long-term consequences (e.g. societal, economic, organizational, ethical, legal). All consequences should be considered understanding their impact in terms of costs and QALYs. However, decision-makers have a twofold need of (1) being knowledgeable of the impacts against the various dimensions; and (2) decide about their relative relevance. Because of that, scholars of health economics and decision science argued that Multi-Criteria Decision Analysis (MCDA) should meet these informative needs and provide decision-makers with more actionable knowledge [17].

MCDA assesses alternative healthcare strategies/medical technologies against a set of established criteria that are identified and agreed on by decision-makers based on their informative needs. The relative relevance of these selected criteria is established through weights agreed among decision-makers. In this view, "utility" is not limited to QALYs and it is calculated as the weighted sum of the scores (i.e. the performance) achieved by alternative healthcare strategies/medical technologies against the criteria. Equation (9.1) shows how value must be calculated according to MCDA.

$$\text{Value} = \sum_{n=1}^{N} W_n * S_n \tag{9.1}$$

where:
N = Number of criteria
W = Weight of the criterion "n"
S = Score against the criterion "n"

Equation (9.1): Determination of Value According to MCDA

The list of criteria can be adjusted over time to meet new informative needs of either other decision-makers (e.g. patient advocacy groups) or specific medical technologies. In this view, the literature is rich in examples of criteria. Among the available proposals, the most interesting is the one adopted by the Italian Lombardy Region in their HTA programme [18]. In this proposal, the domains of the Core Model developed by EUnetHTA (that has been described in the section above) have been matched with the criteria developed by EVIDEM to support the appraisal. Table 9.3 shows this match by grouping the EVIDEM criteria (right column) against the domains identified by the EUnetHTA Core Model (left column). While these criteria are relevant and exhaustive for decision-makers at the national/regional level, they are not sufficient for decision-makers at the hospital level. For instance, these criteria do not meet the informative needs about the organizational impacts in terms of new clinical processes, learning curves, resistance to change, etc. All these aspects are better covered in Hospital-Based HTA models (see the next section). Once criteria have been defined and agreed by decision-makers, their relative relevance must be established. Even if there are not reference guidelines about how to define the relative relevance, scholars of decision science agree that the most simple and

Table 9.3 Match between core model domains and EVIDEM appraisal criteria

Current use	• Guidelines & Good practice recommendations • Limitations of alternative technologies in use
Technology	• Completeness and consistency of documentation • Relevance and validity of documentation • Description of technology and benefits areas
Safety	• Improvement of safety and tolerability
Effectiveness	• Improvement of effectiveness and efficacy • Improvement of patient-related outcomes
Organization and economics	• Financial impact on health system • Cost-effectiveness • Impact on other spending
Social, ethical, and legal analysis	• Disease severity • Size of population • General healthcare goals • Coherence with regional planning

valuable method is allocating 100 points among the different criteria (Table 9.4). This allows decision-makers pointing out which criteria are the most relevant. According to the fairness principle (legitimacy theory), weights should be made explicit and known from those that will be evaluated. The authors of this chapter argue that making weights explicit and stable for a medium-long period (e.g. 5 years) can positively contribute to the competitiveness of the MedTech industry with the result that developers and producers of medical technologies will know in advance which criteria (and relative weights) will be used to assess their innovative proposals, allocating their R&D efforts only to those that will have better chances to be positively evaluated.

The last step is the assessment of the alternative healthcare strategies/medical technologies against the agreed criteria. This assessment must be carried out by reviewing all available evidence that has been synthesized in HTA reports. The complexity of this phase relies on the fact that current HTA reports do not cover all assessment criteria and decision-makers might be left without relevant pieces of information. In this view, the agreement of what criteria are the most relevant will contribute positively on the production of relevant evidence, starting from the clinical studies, whose case report form might be enlarged to cover all assessment criteria. The alignment between the informative needs of decision-makers and what researchers collect from the field could significantly benefit the capability of the healthcare system to generate value through the allocation of the limited financial resources only to those healthcare strategies/medical technologies that proved to be the most promising.

From an operative point-of-view, there are no (again) reference guidelines about who and how should give the "scores". About the "who", there are two relevant experiences. On the one hand, the EVIDEM Collaboration suggests that experts of the clinical domain under assessment should score the alternative healthcare strategies/medical technologies. The rationale is that these experts are knowledgeable and could provide expert opinions. On the other hand, the Lombardy Region in Italy creates a group of experts of different disciplines (e.g. medicine, nursing, clinical engineering, economics, law) to maximize the legitimacy of the appraisal exercise. About the "how", the most relevant experience is from Canada [19]. They suggest (see Table 9.4) to score on a Likert scale that goes from "−3" (extremely negative relative performance) to "+3" (extremely positive relative performance).

The "relative value" generated by the medical technology under assessment with respect to its comparators would range from "−3" to "+3"—after normalizing the weights from 0 to 1 (i.e. dividing by 100). As for Cost-Utility Analysis, policymakers must define an acceptance threshold. There are no significant experiences about this; however, the authors of this chapter argue that a threshold around 1.75 might constitute a fair reference.

Table 9.4 Example for parameters and their weights and scores for MCDA

		Scores						
		Extremely negative relative performance	Negative relative performance	Partially negative relative performance	Similar performance	Partially positive relative performance	Positive performance	Extremely positive relative performance
Criteria	Relative weight	−3	−2	−1	0	+1	+2	+3
Guidelines recommendations								
Limitations of alternative technologies								
Completeness of documentation								
Relevance and validity of documentation								
Description of technology								
Improvement of Safety and Tolerability								
Improvement of Effectiveness/ Efficacy								
Improvement of patient-related outcomes								
Financial Impact on Health System								

Cost-effectiveness										
Impact on other expenses										
Disease severity										
Size of population										
General Healthcare Goals										
Coherence with regional planning										
	100 points									

9.1.6 Social Return on Investment (SROI) in Healthcare

The rising doubts about Cost-Utility Analysis (CUA) have incentivized the exploration of alternative approaches to the measurement of the value generated by alternative healthcare strategies/medical technologies. In the previous section, the growing interest in MCDA has been illustrated. Another direction of exploration is offered by the Social Return on Investment (SROI) that has received significant attention in the field of social enterprises and non-profit organizations.

SROI is a method used to account for "social value" when evaluating investments that are oriented to generation of value for the society (like healthcare). This method goes far beyond the traditional economic evaluation tools (like Cost-Benefit Analysis, CBA), by considering the value that is produced for multiple stakeholders in three main domains: economic, social, and environmental [20]. In this view, SROI can be a relevant method in the context of advocacy for investments for health [21]. SROI goes beyond the limitation of the traditional Return on Investment (ROI) that accounts only for shareholder value (i.e. the pecuniary value) and overlooks the positive/negative externalities that might advance the public good [22]. In light of that, evaluators should include a wider range of benefits, complementing the economic domain with the environmental and social ones. SROI is the ratio between the net present value of the whole range of benefits and the net present value of the resources invested [23]. This concept of SROI has been applied at the beginning by philanthropic foundations to demonstrate the impact of the social programmes that have been funded [24]. From this, the concept of SROI has undergone several revisions and it is still at the centre of an intense academic debate about its superiority with respect to CUA and CBA.

So far, to the best knowledge of the authors of this chapter, generally accepted practices to apply the SROI to the assessment of alternative healthcare strategies/medical technologies do not exist and different approaches are in place. However, the five main steps described by Nicholls and Lawlor [25] can be taken as a reference guideline. These steps will be described briefly in the following.

First, it is necessary to establish the scope and identify the most relevant stakeholders. The scope of a SROI analysis is an explicit statement about the boundaries of what will be included. It requires to consider the purpose, the audience, the background, the resources, the range of activities to focus on, the period over which the intervention will be (or has been) delivered, whether the analysis is a forecast or an evaluation. Relevant stakeholders (i.e. people or organizations that are affected or do affect the initiative under evaluation, either positively or negatively) are beneficiaries, caregivers, patient advocacy groups, the healthcare system, the pharmaceutical/MedTech industry, insurance companies, the economic system of the region under analysis, NPOs (Non-Profit Organization) and NGOs (Non-Governmental Organization), municipalities, etc.

Second, outcomes must be mapped. Outcomes are the positive/negative consequences of the initiative under evaluation. The outcomes perceived by each stakeholder must be recognized. The most recurring outcomes in healthcare are increased

quality of life, social inclusion, increased income, savings for beneficiaries, savings for the healthcare system, savings for the society, increased productivity because of improved health status. In this step, it is required also to recognize the inputs, i.e. what stakeholders are contributing to making the initiative feasible and successful. Typical inputs are the initial costs (fixed and non-fixed assets purchase), personnel training costs and labour costs, maintenance costs, renovation costs, overhead and administration costs, operational costs.

Third, outcomes must be valorized. Outcome indicators represent a preliminary step to monetize the identified outcomes. By multiplying the value of each indicator for its unitary monetary value, the monetary value of each outcome can be obtained. To reach this purpose, financial proxies based on methods such the Willingness-to-Pay (WTP) or the Human Capital are used to estimate the social value of non-traded goods.

Fourth, the impact must be established. The task is estimating how much of the outcomes would have happened anyway without the initiative under evaluation and what proportion of the outcome is generated by the initiative. Therefore, four main elements need to be quantified into percentages: deadweight (amount of outcome that would have happened even if the initiative had not taken place), displacement (how much of the outcome displaced other outcomes—e.g. reducing crime in one area may displace criminal activity to another area), attribution (how much of the outcome was caused by the contribution of other organizations or people), and drop-off (mitigation or decay of the outcomes over time).

Fifth, SROI can be calculated. The Net Present Value (NPV) of outcomes is calculated by adding up all benefits and by subtracting any negative effect in different periods through a discount rate (a reference value is equal to 5%). The net impact of the initiative under analysis can be calculated by deducting the four percentages pointed out previously from the NPV of the outcomes. The SROI ratio is computed by dividing the NPV of the net impact by the Present Value of inputs. Finally, a sensitivity analysis should be carried out to explore how the value generated might vary accordingly to some assumptions.

Many scholars of health economics and health policy claimed that SROI looks like CBA. While both methods translate consequences into monetary terms, SROI, more than CBA, can capture the perspectives of different groups of stakeholders [26].

In this view, SROI has been acknowledged as an extension of the traditional CBA that incorporates the broader socio-economic and environmental outcomes [27]. In the next years, an increasing number of applications of the SROI method to the assessment of alternative healthcare strategies/medical technologies is expected, as well as a discussion about the informative power of SROI assessments with respect to MCDA ones.

9.2 Disinvesting for Investing in Healthcare

The financial sustainability of the national healthcare systems of the most developed countries as we know them nowadays cannot be taken from granted for the next years. The "perfect storm" that has been generated by the combination of population ageing, non-communicable chronic diseases, GDP (Gross Domestic Product) stagnation, medical technology booming, citizen empowerment, etc., pointed out the need for new socio-technical paradigms for healthcare delivery and innovation management. The progressive shrinking of the available financial resources for the adoption of innovative medical technologies—e.g. medical devices, equipment, cancer drugs, digital solutions—enlarges the gap between what healthcare professionals and citizens would need and what they can have available in their daily practice. Innovative medical technologies, that proved to be value-for-money and safe, should be adopted as soon as possible to maximize the generation of societal benefits. Innovation should not be slowed down, or its adoption procrastinated.

In this view, the very question is how to sustain the adoption of novel medical technology in a context of shrinking financial resources. An interesting solution stemmed out from the reasoning about disinvesting for investing. This approach—that has been applied in the USA and Canada, even if done with different methods—grounds on the opportunity to save money from a medical technology already in place to fund the adoption of another medical technology that offers more value.

The example in Fig. 9.7 can clarify the theoretical underpinning of this approach.

Five innovative medical technologies are ready to enter the market. Which one should be prioritized in case of limited financial resources? This problem can be

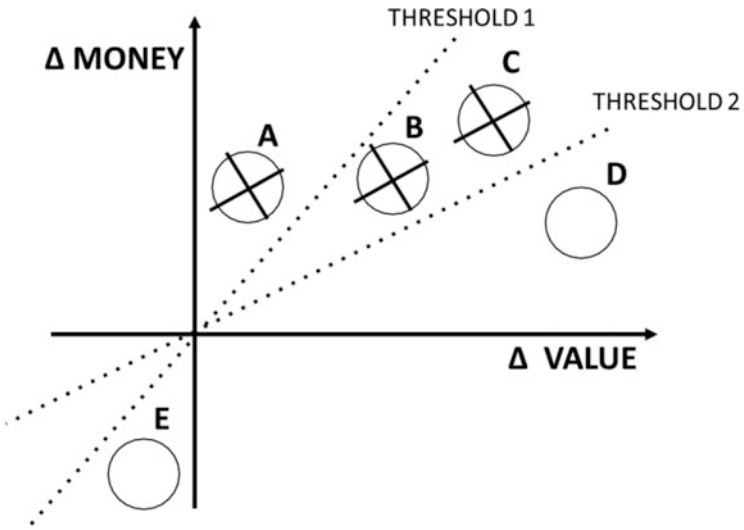

Fig. 9.7 Adopting medical technology E to fund the adoption of medical technology D. For details, see text

approached using a cost-utility analysis. In this view, the five innovations are benchmarked in terms of their incremental cost-utility ratio. The selection is done defining a threshold. In the case of threshold 1, technology A should be rejected because the value—in terms of quality-adjusted life years—is not enough compared to the necessary costs. In the case of a more selective threshold, as threshold 2, technologies B and C would be rejected, too. The choice should go on technology D. But what, if the costs required by technology D do not meet the available financial resources? One opportunity might be to adopt technology E, too. Technology E is very peculiar because it offers the opportunity to save money with respect to the current comparator in daily practice while reducing—on a limited amount—the value for this group of patients. Saving these costs will offer the opportunity to fund the adoption of technology D (looking at Fig. 9.7, costs saved by technology E are pretty much the costs needed to run technology D). In this view, by disinvesting in the comparator of technology would be possible to invest in technology D. Following this line of reasoning—and broadening the discussion about this method—another opportunity is to disinvest from all those medical technologies that allow saving a significant amount of financial resources while limiting the reduction of value for patients. In this way, savings would guarantee the opportunity to invest in a larger number of innovations. *Ça va sans dire*, that this approach might raise ethical concerns. Our opinion is that this approach is rational and ethical because it tries to move the perspective from a group of patients to society. A priority of decision-makers in healthcare should be the maximization of societal benefits against the available resources. In this view, the limited reduction of benefits for a group of patients is more than compensated by the increased benefits for other groups of patients, on the same line of reasoning of the League Tables that compare the ICUR of different technologies/practices [16].

The theoretical arguments found application in real life into two relevant experiences.

On the one hand, the *Choosing Wisely* movement in the USA applied these concepts through a consensus-based approach based on expert judgement elicitation. The scientific associations of the different medical disciplines supported a debate about the members of the association, about the identification every year of five medical technologies/practices to be eliminated to generate enough savings for adopting emerging medical technologies. In this case, the responsibility to identify those technologies/practices to be eliminated is left to the discussion—and agreement—among experts who might evaluate the impacts of such decisions. Moreover, it is interesting the repetitive nature (year after year) of this discussion that confirms the need for healthcare professionals to identify a systematic approach to get access to innovative technologies also in a context of shrinking financial resources.

On the other hand, the Vancouver Coastal Health Authority in Canada designed and implemented an interesting disinvestment programme in 2010 to meet the constraints on the available financial resources and to fund the adoption of new medical technologies. In their well-known study, Mitton et al. [19] described in detail this unique experience thus making possible its application in other healthcare systems. The method grounds again on expert judgement elicitation. However, the

main difference relies on the development of a quantitative approach based on multi-criteria decision analysis (MCDA) to support prioritizat ion and decision-making. In this view, the value of different practices/medical technologies is the result of performance scores against agreed assessment criteria that are weighted according to their relative relevance. Engaging with experts is necessary to legitimize the process, concerning the identification of the assessment criteria and their weight. By applying this MCDA-based approach, the Vancouver Coastal Health Authority in Canada has been able to identify 42 practices/medical technologies to dismiss in order to meet the budgetary constraints while minimizing the lost value for citizens. Moreover, they have been able to identify additional disinvestment opportunities to save money to be reinvested in new practices/medical technologies.

These experiences confirm the applicability in real contexts of the theoretical arguments developed about disinvestment as a strategy for sustaining the adoption of innovations in healthcare. As told, healthcare cannot progress without the systematic adoption of new medical technologies that proved to be value-for-money and safe. In this view, policymakers of the most developed countries should explore the opportunity to design and implement strategies that combine disinvestment from those practices/medical technologies that claim to generate value—but they do not generate enough value actually—to reinvest these savings into practices/medical technologies that can improve equity among citizens, as described in the theoretical example in Fig. 9.7.

9.3 Technology Assessment in Hospitals

9.3.1 The Linkage Between Technology Assessment and Hospital Strategy

Hospitals are at the forefront of technological innovation in healthcare [28]. Hospital professionals scan systematically the horizon in search of novel medical technologies that might contribute to generate additional benefits in terms of effectiveness, efficiency, and safety. In this view, they need clear guidelines and instruments to select only the most promising innovations among the many that go to market and avoid the risk to invest in technologies whose claim of value are not proven.

Therefore, hospitals must own competencies and knowledge to assess medical technologies. In countries—such as Italy—where a reference national HTA Agency is missing, hospitals must be in the possibility to make evidence-based decisions concerning novel medical devices, equipment, digital technologies, etc. Even in those countries—such as England, Denmark, and Canada—where there is a reference national HTA Agency, hospitals must assess medical technologies for several reasons. **First**, not all novel medical technologies that might be of interest for hospitals are evaluated at the national level because of a prioritization strategy. **Second**, HTA reports offer conclusions and recommendations that are often general

and far from the local-sensitive questions of hospitals. **Third**, new and expensive medical technologies arrive mainly at university hospitals which have immediate pressure from manufacturers, professionals, and patients to adopt them. Only later this need reaches the national agenda, where the assessment timeframe is often longer. **Finally**, hospitals have a direct interest (medical, economic, organizational) to push and speed-up both the assessment and the reimbursement of novel technologies at the national level (e.g. medical procedures), sharing their results as well as their HTA reports.

Given that hospitals must own competencies and instruments to assess novel medical technologies, technology assessment should be a relevant phase within a broader responsibility on technology management. Four synergic phases are typically in place. **First**, technology selection, whose aim is to (1) select those technologies that might better support hospital processes, and (2) define what is the most correct timing for the adoption of new medical technologies. **Second**, technology allocation, aimed at defining the best allocation of the available financial resources (1) between old (maintenance) and new (acquisition) medical technologies, and (2) among different departments (homogeneous vs focused distribution of resources). **Third**, technology assessment, that must support hospital decision-makers through an evidence-informed, multidimensional assessment of medical technologies (effectiveness, safety, costs, organizational impact, professional competencies needed, uncertainty etc.) that have been identified in the previous phases. **Finally**, technology management should be aimed at putting in place operative procedures for (1) maintaining and developing the medical technology stock; (2) guaranteeing safety to both hospital professionals and patients; and (3) reducing risks. These four phases are typically under the responsibility of the Clinical Engineering Department because clinical engineers are familiar with medical technologies and managerial instruments.

Technology assessment in hospitals—better known as Hospital-based HTA (HBHTA)—is strictly connected with the hospital strategy. The value of a novel medical technology is the result of how and to what extent this technology might contribute to putting in place the hospital strategy. Hospitals are very different (teaching vs no-teaching, large vs small size, large city vs rural, private vs public, general vs specialized, etc.) and have very different strategies. In this view, the same innovation might be relevant for hospital A and irrelevant for hospital B, because these hospitals are different and are pursuing different strategies. Hospitals that implement HBHTA procedures cannot rely on *one-size-fits-all* organizational solutions but must define a tailored one.

Following this line of reasoning, past research showed that hospitals follow at least three different strategies when they adopt medical technologies [29]. They are (1) Profit Maximization; (2) Technology Leadership; and (3) Clinical Excellence. Each strategy significantly affects the relative relevance of the assessment criteria, prioritizing some criteria—i.e. expected results—with respect to other ones. Therefore, the same medical technology can be adopted by hospital A and rejected by hospital B. In the followings, the most relevant assessment criteria for each strategy are reported.

Hospitals with a profit maximization strategy are expected to adopt novel medical technologies that enable them to generate an economic return and to improve the income statement (revenues against costs). In this view, the most relevant assessment criteria are (1) investment size; (2) savings of operating costs; and (3) additional revenues. Hospitals with a technology leadership strategy are expected to adopt novel medical technologies that allow them to be "technology leaders" and improve their external image to attract doctors and patients. In this view, the most relevant assessment criteria are (1) technology innovativeness; (2) chance of being the "first adopter"; (3) contribution to research and novel knowledge development; (4) contribution to the development of new services; and (5) physicians' pressure. Finally, hospitals with a clinical excellence strategy are expected to adopt novel medical technologies that optimize the satisfaction of clinical needs, regardless of financial considerations, competitive advantages and prestige suggest other choices. Coherently, the most relevant assessment criteria are (1) burden of disease; (2) potential number of beneficiaries; (3) clinical effectiveness; (4) safety; and (5) completion of the current portfolio of health services. As seen, the assessment criteria are expected to be significantly different and linked to the specific strategy that the hospital is putting in place. It is important to clarify that even if the above-cited assessment criteria are the most relevant for each strategy, this does not mean that criteria from other strategies are overlooked completely. For instance, hospitals that aim at profit maximization do not overlook completely criteria, such as clinical effectiveness and safety, but their attention is focused on other dimensions of impact.

9.3.2 The Organizational Arrangements for Technology Assessment in Hospitals

Hospitals implement different, tailored organizational arrangements to support HBHTA [30]. The choice of the most adequate organizational arrangement is related to the maturity of the HBHTA practice. While hospitals that are at the beginning of their experience with HBHTA might prefer a simple and efficient organizational arrangement, hospitals with more legacy might prefer more sophisticated configurations. The variety of organizational arrangements can be synthesized in a two-dimension matrix (Fig. 9.8).

The horizontal dimension deals with the so-called "focus of action" for HBHTA. The focus of action can be either "clinical practice" or "managerial decision-making". The former approach focuses on the assessment of novel medical technologies concerning the expected impacts on mainly effectiveness and safety. Hospitals are at the forefront of technological innovation and many of the technologies that are under assessment do not have a full body and level of evidence. This might be the case for medical devices. The priority for hospital professionals is that novel technologies, with limited evidence, are at least safe and effective for patients, echoing Hippocrates's oath "*first no harm*". The latter approach deals with a more

		Focus of action	
		Clinical Practice	*Managerial decision-making*
Organizational Complexity	*High (team-group-unit)*	"Internal Committee" Model	"HTA Unit" Model
	Low (individual)	"Ambassador" Model	"Mini-HTA" Model

Fig. 9.8 Different organizational arrangements for hospital-based HTA

comprehensive assessment of novel medical technologies, including other criteria such as organizational impacts, investment size and running costs, etc. This might be the case for equipment or digital technologies. Equipment (e.g. surgical robot, diagnostic system) is a capital-intensive technology and hospitals managers must forecast the economic impact—and sustainability over time—of the adoption of such technology (see e.g. Chaps. 5, 6, and 11). Digital technologies reshape processes, practices, and behaviours; in this view, forecasting the expected organizational impacts is a priority for hospital managers and professionals.

In Fig. 9.8, the vertical dimension deals with "organizational complexity", that is measured as the number of professionals involved in HBHTA activities. In hospitals where a single professional is involved, organizational complexity is "Low". On the contrary, in hospitals where a group of professionals is involved, the organizational complexity is "High".

Combining the horizontal and the vertical dimensions, four main different archetype organizational arrangements—labelled as Models—can be identified.

The "Ambassador Model" is a low-complexity approach focused on clinical practice (see also Chap. 3). This approach is the simplest and might be of interest for hospitals that are at the beginning of their journey towards HBHTA. In a nutshell, one (or more) doctor(s) who is recognized as an "opinion leader" on technology assessment is appointed as ambassador of the "HTA message" inside the hospital, with the purpose to persuade other physicians that novel medical technologies should be assessed before deciding to adopt them. Hospital professionals must assess these technologies against safety and effectiveness criteria to inform decision-making.

The "mini-HTA Model" is a low-complexity approach that covers clinical and managerial domains of assessment. This approach, developed in Denmark in 2006, is widely adopted across Europe, even if with variants. Examples are the GANT

method in Spain and MCDA-based methods in Italy. The original version of mini-HTA is a checklist of 26 open questions on four domains (technology, patient, organization, economics) that allow hospital decision-makers to gather a comprehensive understanding of the main impacts concerning the adoption of the novel medical technology. The method is of low complexity because a single hospital professional—typically a clinical engineer—is the main orchestrator of data collection from all professionals who own relevant information and data analysis. The main advantage of this method is that it is efficient and simple, meeting the needs of HBHTA. Vice versa, the main disadvantage concerns the usage of open questions that often do not allow to collect complete and high-quality information.

The "Internal Committee Model" focuses on clinical practice and engages with a large number of hospital professionals. The committee is a permanent organizational structure composed mainly by physicians and clinical engineers who add this task to their daily responsibilities. The focus of their analysis is safety and effectiveness. Committees are very heterogeneous in size and competences and, surprisingly, past research did not provide hospital managers with clear guidelines and advice about how to design high-performing HTA committees. A recent study by Foglia et al. [31] runs a quasi-experiment to gather some insights. They found that (1) quality of HBHTA reports increases where internal committees are composed of professionals from different specialities; (2) size and multi-speciality of the internal committee should not grow too much to avoid inefficiencies due to increased coordination efforts; (3) trust within the members and the attendance of HTA training are key factors to improve performance of HBHTA committees.

Finally, the "HTA Unit Model" is the most complex and expensive organizational arrangement for HBHTA. In this case, a permanent organizational structure composed of hospital professionals from different specialities who are fully dedicated to HTA-related activities is created. With respect to internal committees, the main advantage is that professionals develop specialized competencies in terms of technology assessment, producing HBHTA reports with higher quality in lower time. Methods such as Cochrane Systematic Review, GRADE analysis, and Total Cost of Ownership (TCO) require specialized competencies that are not typically owned by all professionals. In this view, professionals who are part of the HTA Unit can stay-updated concerning HTA methods and tools.

The main disadvantage is that this method is very expensive because professionals are dedicating 100% of their time to technology assessment. This might make sense for those hospitals whose strategy is technological leadership, and the adoption of emerging medical technologies is very frequent.

9.3.3 Frameworks for Technology Assessment in Hospitals

While the production of HTA reports at the national/regional level follows established and agreed guidelines, HBHTA reports differ significantly. The reasons are, on the one hand, that HBHTA is a more recent research stream and less research

has been paid so far to this topic by scholars of health economics and health technology assessment, and, on the other hand, the many differences among hospitals—as seen in the previous sections—in terms of strategy, informative needs, and HBHTA practices. Even if widely accepted reference frameworks for HBHTA do not exist, mini-HTA can be assumed as a relevant cornerstone. This method made clear that HBHTA must meet two relevant requirements of any technology assessment exercise. **First**, an assessment must be evidence-based. **Second**, an assessment must consider different domains and not just effectiveness. In this view, the emerging HBHTA frameworks share the same theoretical assumption that both hospital managers and professionals must have been provided with clear guidelines and advice about which criteria refer to for collecting evidence and informing decision-making [32].

Within the variety of HBHTA frameworks that are emerging, two of them are particularly relevant to be discussed. The first one is the IMPAQHTA framework (see Table 9.5) [31]. This approach is interesting because it has been developed to bridge the assessment of medical technologies between national/regional and hospital levels. Grounding on the Core Model developed within the EUnetHTA collaboration, this approach confirms its dimensions for assessment and specify both sub-dimensions and measures in the peculiar context of hospitals (Table 9.5). Sharing the same architecture and technical language, this approach might facilitate information exchanges between the different levels of the healthcare ecosystem and narrow-down the current gap. In particular, the national/regional level is expected to benefit from the assessments run in hospitals that, even if with partial respect to the national/regional level, are timelier and context based.

The second HBHTA approach worth to be discussed grounds on the Innovation Management literature and offers an original point-of-view on how medical technologies should be assessed in hospitals [28]. Based on the legacy of value-risk matrixes, Lettieri and Masella [28] developed an original framework to inform technology assessment in hospitals. Medical technologies should be assessed against two dimensions (Fig. 9.9).

The vertical dimension deals with the concept of "value", i.e. the expected capability of the novel technology to generate benefits in terms of (1) social value creation; (2) economic value creation; and (3) knowledge creation. Table 9.6 crystallizes the criteria to measure expected benefits. Even if with different terminology, these three dimensions of value creation echo the three main strategies hospitals might implement when adopting novel medical technologies. Coherently, many criteria remind to those identified for the different strategies.

The horizontal dimension addresses the concept of "uncertainty", i.e. the possibility that expected benefits might not be achieved. The adoption of a novel medical technology is an investment, i.e. present financial resources are employed to generate additional value in the long term. However, decision-making is taken in the context of bundled information about the future. This means that decision-makers must evaluate and discuss the uncertainty of results. In this framework, the "level of sustainability" means the probability that expected benefits will materialize. The capability of a hospital to achieve expected results is a function of five different

Table 9.5 IMPAQHTA dimensions and sub-dimensions developed within Lombardy Region in Italy

Dimensions	Rational	Sub-dimensions	Quantitative measures
General relevance	Scientific and empirical evidence analysis aimed at providing a comprehensive description of the general relevance for both the technology and the population	Quality of scientific evidence	Considering four dimensions (quality of scientific evidence concerning the comparators, consistency, completeness, and utility of the results), using a four-item evaluation scale derived from "Get Five" approach: the higher the average measure, the preferable the technology
		Description of the pathology and the related technologies	• Prevalence or incidence of the pathology affecting the population related to the catchment area of reference (local, regional, national, etc.) • Number of potential patients treated with the innovative technology, divided by the population affected by the specific analysed disease
Safety	This dimension leads to the evaluation of: • adverse events, mortality, or morbidity • consistency of the innovative technology with health and safety policies • consistency of the innovative technology with its guidelines or protocols	Seriousness of adverse events (mild, moderate, or severe adverse events)	• Incidence of adverse events, divided by the population treated with the technology • Mortality and morbidity rates • Administration of a qualitative questionnaire aimed at rating the consistency of the innovation concerning: (1) health and safety policy and (2) guidelines and protocols, using a 7-item Likert Scale (the higher the average measure, the preferable the technology)
Efficacy	Analysis of the efficacy data retrieved from the scientific literature, referring to how the innovative technology performs in the clinical trials	Efficacy data	i.e. mortality rate related to the use of technology, percentage of success of the treatments compared, sensitivity or specificity of diagnostic images, etc. revealed in randomized controlled trial or literature evidence

(continued)

Table 9.5 (continued)

Dimensions	Rational	Sub-dimensions	Quantitative measures
Effectiveness	Analysis of the effectiveness data of the innovative technology, based on the hospital setting, referring to how innovative technology works in real-world evidence and community settings	Effectiveness data	i.e. mortality rate related to the use of technology, percentage of success of the treatments compared, sensitivity or specificity of diagnostic images, etc. based on the real hospitals setting in which technologies are adopted
Economic financial Impact	Economic and financial impact evaluation, considering: 1. the healthcare process considered, 2. the new technology budget impact implementation, and 3. the number of resources spent about effectiveness and efficiency outcomes	Activity-Based Costing (ABC) Analysis	Process costs comparison considering all the direct costs, and, where possible, the indirect ones (the lower the economic value, the preferable the technology)
		Complete Health Economic Evaluation	Cost-effectiveness, cost-utility, and cost-benefit analysis, calculated as pathway or process costs divided by the outcome indicator (measured with physical, humanistic, or economic units)
		Budget Impact Analysis	Target population multiplied by the pathway or process costs (considering either the ceasing or the incremental costs, comparing at least two different scenarios)
Equity	Evaluation of all aspects related to the introduction of the innovative technology, considering the perspective of the patient, and the following aspects: • access to care on a local level • access to care for the target treated population, including persons of a legally protected status • hospital waiting lists improvement • invasiveness	Equity data	Administration of a qualitative questionnaire aimed at rating the variables related to the equity dimensions, using a 7-item Likert Scale (the higher the average measure, the preferable the technology)
Legal, social, and ethical impact	Analysis of the social and ethical issues that innovative technology could have on the system, considering the	Legal aspects	Administration of qualitative questionnaires aimed at rating the variables related to the legal, social, and

(continued)

Table 9.5 (continued)

Dimensions	Rational	Sub-dimensions	Quantitative measures
	following aspects: • customer satisfaction • productivity loss • market regulation		ethical dimension, using a 7-item Likert Scale (the higher the average measure, the preferable the technology)
		Social and ethical Impact	Reduction in productivity loss (in terms of days, hours, or minutes, evaluated considering the patient's gross monthly income)
Organizational impact	Evaluation of organizational changes occurring after the innovation implementation. The qualitative impact investigates the perception of clinicians, and health professionals, involved in this innovation change management. The quantitative impact aimed at the determination of the investment needed if organizational changes occur. The following aspects are investigated: • additional people • training courses • meetings needed to communicate the technological change • additional equipment, or spaces needed • learning time of the innovative technology	Quantitative impact	Ceasing or incremental costs evaluation and forecast, related to the adoption of the innovative technology in clinical practice, compared with the standard one, considering additional persons, training courses, additional equipment, spaces, or rooms needed
		Qualitative impact	Administration of qualitative questionnaires aimed at rating the variables related to the organizational dimension, using a 7-item Likert Scale (the higher the average measure, the more preferable the technology) both in the short-term (12-month) and in the long-term (36-month) period

IMPAQHTA IMPlementation of A Quick hospital-based HTA

factors. They are (1) economic sustainability; (2) organizational sustainability; (3) technological sustainability; (4) resource sustainability; and (5) context sustainability. Table 9.7 crystallizes the main criteria.

Even a cursory analysis of this framework would make clear why different hospitals might make different decisions concerning the same novel medical technology. While some criteria refer to factors that would receive a similar assessment from different hospitals (e.g. the coherence to the legal framework, the existence of agreed guidelines, the position in the life cycle), other factors are hospital-specific (e.g. technology acceptance among physicians, coherence to the current portfolio of technologies). In this view, hospitals must develop capabilities and competencies for

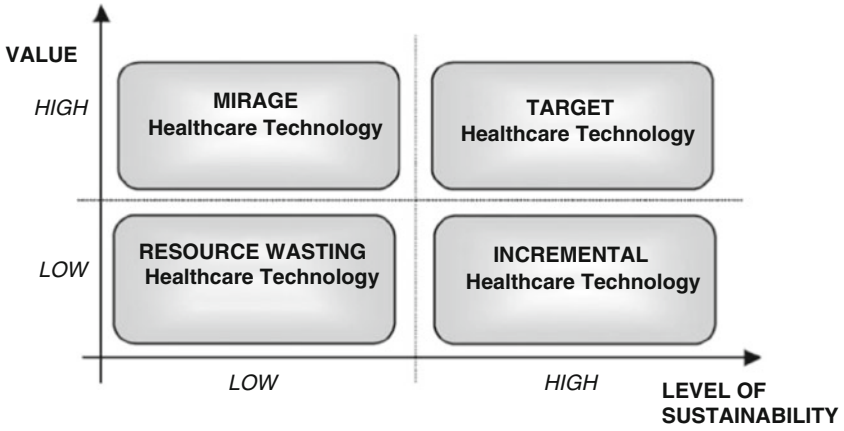

Fig. 9.9 The value/sustainability framework for HBHTA

Table 9.6 Measuring "Value" in hospitals

Perspective	Benefits	Measures
Short-term	Social value creation	Clinical effectiveness
		Patient's or family's satisfaction
	Economic value creation	Revenue generation
		Cost savings
		Gains in either image or reputation
Long-term	Knowledge creation	Development of new health services
		Development of new healthcare technologies
		Building-up of new communities of knowledge

Table 9.7 Measuring "Level of sustainability" in hospitals

Sustainability factor	Measures
Economic	Degree of self-funding
	Ratio "fixed/variable costs"
	Coherence to strategic goals (top managers' commitment)
Organizational	Technology acceptance among physicians
	Uncertainty in clinical practice
Technological	Positioning in the technology life cycle (TRL)
	Coherence to the current portfolio of technologies
Resource	Training intensity
	Coherence of human and physical resources
Context	Coherence to the current legal framework
	Coherence to the generally accepted ethics (legitimacy)

technology assessment also where a national HTA Agency does exist because findings at the national/regional level must be contextualized at the local level.

9.3.4 Acceptance of Innovation in Hospitals

Many medical technologies might disrupt current practice. In this view, physicians' acceptance of these innovations is a salient criterion to measure organizational sustainability, as discussed in the previous section. Past research has gathered a significant body of evidence concerning physicians' resistance—or indifference—to novel medical technologies. A paradigmatic example is offered by telemedicine. The diffusion of ICT-enabled innovations—e.g. electronic medical records, "televisit-solutions"—has fallen far behind expectations, and physicians are still not championing such innovations. These examples make clear that physicians' acceptance is of paramount importance when assessing the adoption of new medical technologies and related changes in their practice and behaviours. Acceptance of innovation—and its antecedents—has been a widely investigated research topic in the last decades. Within an extensive body of literature, two main streams might be crystallized.

On the one hand, scholars of applied psychology and information science developed theoretical explanations grounded on the assumption that "acceptance" is the result of the rational evaluation made by single individuals—in this case, hospital professionals—of pros and cons generated by specific innovations. Coherently to this premise, a variety of user acceptance models, derived from the seminal Technology Acceptance Model (TAM) [33–36], have been generated in the last years (e.g. TAM2, UTAUT). Although there are some differences among the models, they all share a "perceived usefulness" and a "perceived ease of use" as the most relevant predictors of physicians' intention to adopt a novel medical technology [37, 38]. Social pressures are also relevant, but only when exercised by peers (i.e. by other hospital professionals) and not by top managers.

On the other hand, scholars of institutional theory and organization science, especially those dealing with professional organizations such as hospitals, developed theoretical explanations that show how a complex bundle of institutional arrangements (i.e. regulations, social norms, and cultural systems) limit and affect individual behaviours. According to these studies, employees' decision to accept novel medical technologies is not the result of rational evaluations, but of the influence exerted by the overarching structures, rules, social norms, and culture in which they are embedded [37]. Past studies within this research streams crystallized three main institutional factors that might shape hospital professionals' intention to engage in new practices or accept novel medical technologies. **First**, professionals are affected by the expectations of the organization (regulative factor). The more the organization provides coercive or persuasive mechanisms that direct or control practice, the more professionals are likely to comply with these expectations in search of retribution. **Second**, professionals are affected by peer influence (normative factor). The more

the meaning system across professionals is cohesive and aligned towards the adoption or the rejection of novel medical technology, the more professionals are likely to adhere to this social norm without challenging it. **Third**, professionals are affected by initiatives and discussions that are run day-by-day in the organization (cultural factor). The more the organization agrees that the current status quo is not adequate anymore and changes are required, the more professionals are likely to contribute to change by enacting innovative behaviours.

Recent research has started to investigate the potential interplay between individual and institutional factors, arguing that the two theoretical perspectives might be merged into a more comprehensive understanding of what drives hospital professionals' acceptance of new medical technologies. De Benedictis et al. [38] gathered evidence that institutional factors affect individual evaluations and contribute to physicians' acceptance of innovative technologies. These findings reinforce the evidence that the same medical technology might be accepted or rejected by different hospitals, and/or within the same hospital by different groups of professionals. In this view, HBHTA cannot overlook the assessment of the factors that might shape professionals' acceptance of novel medical technologies, also to design and implement strategies that might facilitate its acceptance. The causal connection between the regulative pillar (i.e. the expectations of the organization) and perceived usefulness clarifies that hospital managers are in the position to affect acceptance through initiatives that make more evident the benefits expected by the adoption of specific innovations.

9.3.5 Government of Technology Assessment in Hospitals

As discussed in the previous section, past research has developed a significant body of evidence about the methods and criteria that should be implemented to assess novel medical technologies in hospitals. Surprisingly, fewer efforts have been paid so far about how to assess the "health status" of the HBHTA process itself. This process is of paramount importance for every hospital and its performance in terms of quality, timeliness, and efficiency should be monitored continuously by hospital managers and clinical engineers. From a pragmatic point-of-view, there is no advantage in designing and implementing sophisticated HBHTA processes that are not able to provide decision-makers with relevant—and reliable—information when they need it. In this view, measuring the current performance of the HBHTA process against targets that have been identified and agreed is necessary for implementing corrective actions where needed.

Let us consider this example taken from real cases. Every month about 30 new requests for the adoption of medical technologies are submitted by hospital professionals. They expect to receive a feedback (either positive or negative) in less than 4 weeks. Internal Committees are composed of about ten hospital professionals who add technology assessment of new proposals on top of their daily activities. HTA Units are composed of about five hospital professionals. How should be designed an

Table 9.8 Performance measurement of HBHTA in hospitals

	Volume	Quality	Time	Efficiency (Costs)
Collection of requests	Number of requests per month	Number of complete requests on the total	Number of requests filled in less than 2 days/person	Time spent in consulting proponents
Assessment of requests	Number of requests assessed on the total	Number of appeals from proponents on total proposals	Number of requests assessed within 30 days on the total	Number of requests that have been filtered
Feedback to proponents	Number of rejections discussed with proponents	Number of proponents that accept rejections	The time between rejection and feedback	Time spent in providing proponents with feedback
Support to decision-makers	Number of HBHTA reports	Number of decisions aligned to the recommendations	The time between the delivery of HBHTA reports and decisions	Time spent by decision-makers on HBHTA reports

HBHTA process to meet hospital professionals' expectations in term of high-quality and timely reports, as well as hospital managers' expectations of efficiency and cost containment of the HBHTA process itself?

Foglia et al. [31] shed first light on how to design a hospital Internal Committee for technology assessment to maximize high quality and efficiency. The European project "AdoptHTA" developed practical guidelines for the design of an HBHTA process in hospitals. Iadanza et al. [39] argued the urgency to implement practices of evidence-based management of medical technologies along with their whole lifespan in hospital. Although the undoubted value of these contributions, research on this topic is still at an early stage and further work is necessary to provide hospital managers and clinical engineers with clear and validated guidelines and advice.

Table 9.8 points out an example of key performance indicators (KPIs) that might be used by hospital managers and clinical engineers to monitor the "health status" of the HBHTA process in place.

The design of the most informative KPIs should be complemented with the crystallization of the most adequate targets. By monitoring the capability of the HBHTA process to meet the expected targets (e.g. assessing all received proposals for novel medical technologies with 30 days) over time, hospital managers and clinical engineers might identify improvement areas and implement the necessary corrective actions (e.g. increased the automatization of the HBHTA process through the adoption of a dedicated informative system).

Conclusion and Emerging Topics About the Assessment of Medical Technologies

In the previous sections of this chapter, some avenues of further development of the assessment of medical technologies have been pointed out. At least four "areas" will witness significant improvements within the next years.

First, the traditional approach based on Cost-Utility Analysis (CUA) will be challenged by Multi-Criteria Decision Analysis (MCDA) and Social Return on Investment (SROI). While CUA is a well-established and robust method, its actual informative power is under discussion. The final goal of any assessment exercise is to support decision-making. If decision-makers systematically do not refer to HTA reports to ground their decisions about the adoption of novel medical technologies, this means that evaluators failed to meet their primary goal.

Second, some domains of HTA need an enhanced degree of operationalization. The most evident example is about the "organization" domain. Both at the national/regional and hospital levels, this domain is not fully translated into relevant criteria to be assessed. The extant literature offers different approaches but none of them has been largely adopted and assumed as a generally accepted practice. This issue is particularly relevant and urgent for those innovations, such as telemedicine, that can unfold their potential value only because of significant organizational redesign and changes.

Third, the governance of the HTA process both at the national/regional and hospital levels requires the design of KPIs and targets to monitor its "health status" over time. These KPIs, where agreed by different committees, will allow bench-learning initiatives—as done currently for the performance of different international/regional healthcare systems—and the crystallization of good practices to be shared. This will guarantee the continuous improvement of such processes.

Fourth, the constantly increasing capability to both collect and analyse real-world data (e.g. from electronic medical records, clinical registries, population-health databases, hospital discharge forms, wearables) offers the opportunity to expand the sources of evidence considered within the HTA reports. At national/regional level, the capability to analyse large-volume administrative data might help to complement what is known from the literature with data from the field. This allows to move the discussion about effectiveness from the evidence collected in clinical studies to that collected in daily hospital practice. At the hospital level, the progressive diffusion of data warehouse might help to better forecast the impacts due to the adoption of a novel medical technology.

Take Home Message

- The healthcare system worldwide needs a reload of the present paradigm in the direction of the value-based healthcare approach.
- Innovation and technology are the key factors for the success of this new approach.
- The introduction of technology and innovation must be deeply analysed using the instruments for the evaluation of investment (and divestment) in healthcare (e.g. HTA, CUA, SROI).

(continued)

- The introduction of innovation should also consider the legitimacy of the taken decision and the impact that the new technologies have on care delivery organizations and society.
- A general and mutual understanding among decision-makers in hospitals is needed in order to allow the introduction of novel medical devices.

References

1. Barlow J (2017) Managing innovation in healthcare. World Scientific, New Jersey
2. Burns LR (2020) The business of healthcare innovation. Cambridge University Press, Cambridge
3. Porter ME, Teisberg EO (2006) Redefining health care: creating value-based competition on results. Harvard Business School Publishing, Boston
4. Moriates C, Arora V, Shah N (2015) Understanding value-based healthcare. McGraw-Hill Education
5. Ferlie E, Montgomery K, Pedersen AR (2016) The Oxford handbook of healthcare management, Oxford University Press
6. Glied S, Smith PC (2013) The Oxford handbook of health economics, Oxford University Press
7. Suchman M (1995) Managing legitimacy: strategic and institutional approaches. Acad Manag Rev 20(3):571–611
8. Zanaboni P, Lettieri E (2011) Institutionalizing telemedicine applications: the challenge of legitimizing decision-making. J Med Internet Res 13(3):e72
9. Goodman CS (2014) HTA 101: introduction to health technology assessment. https://www.inahta.org/wp-content/uploads/2014/09/HTA-101_Goodman_2004.pdf
10. EUnetHTA "HTA Core Model Version 3.0". https://eunethta.eu/wp-content/uploads/2018/01/HTACoreModel3.0.pdf
11. Kristensen FB, Lampe K, Wild C, Cerbo M, Goettsch W, Becla L (2017) The HTA Core Model®—10 years of developing an international framework to share multidimensional value assessment. Value Health 20(2):244–250
12. Packer C, Simpson S, Terezinha de Almeida R (2015) EUROSCAN international network member agencies: their structure, processes, and outputs. Int J Technol Assess Health Care 31 (1-2):78–85
13. Drummond MF, Sculpher MJ, Claxton K, Stoddart GL, Torrance GW (2015) Methods for the economic evaluation of health care programmes. Oxford University Press
14. Cabrera CI, Ning AY, Cai Y, D'Anza B (2020) Systematic review of telehealth cost minimization for patients and health systems in otolaryngology. Laryngoscope
15. Cutti AG, Lettieri E, Del Maestro M, Radaelli G, Luchetti M, Verni G, Masella C (2017) Stratified cost-utility analysis of C-Leg versus mechanical knees: findings from an Italian sample of transfemoral amputees. Prosthetics Orthot Int 41(3):227–236
16. Maynard A (1991) Developing the health care market. Econ J 101:1277–1286
17. Marsh K, Goetghebeur M, Thokala P, Baltussen R (2017) Multi-criteria decision analysis to support healthcare decisions. Springer
18. Radaelli G, Lettieri E, Masella C, Merlino, Strada A, Tringali M (2014) Implementation of EUnetHTA core Model® in Lombardia: the VTS framework. Int J Technol Assess Health Care 30(1):105–112
19. Mitton C, Dionne F, Damji R, Campbell D, Stirling B (2011) Difficult decisions in times of constraint: criteria based resource allocation in the Vancouver coastal health authority. BMC Health Serv Res 11:169

20. Millar R, Hall K (2013) Social return on investment (SROI) and performance measurement: the opportunities and barriers for social enterprises in health and social care. Public Manag Rev 15(6):923–941
21. Dyakova M, Hamelmann C, Turatto F, Volker T (2017) Social return on investment—accounting for value in the context of implementing Health 2020 and the 2030 Agenda for Sustainable Development. https://www.euro.who.int/en/countries/italy/publications/social-return-on-investment-accounting-for-value-in-the-context-of-implementing-health-2020-and-the-2030-agenda-for-sustainable-development-2017
22. Maas K, Liket K (2011) Social impact measurement: classification of methods. In: Environmental management accounting and supply chain management. Springer
23. Gargani J (2017) The leap from ROI to SROI: farther than expected? Eval Program Plann 64: 116–126
24. Westall A (2004) Social return on investment: valuing what matters. Findings and recommendations from a pilot study. London, New Economics Foundation
25. Nicholls J, Lawlor E (2008) A guide to social return on investment: The SROI network. Accounting for value. https://commdev.org/pdf/publications/Measuring-Value-A-Guide-to-Social-Return-on-Investment.pdf
26. Self P et al (2015) Econocrats & the policy process: the politics & philosophy of cost-benefit analysis. Macmillan International Higher Education
27. Arvidson M, McKay S (2013) Valuing the social? The nature and controversies of measuring social return on investment (SROI). Voluntary Sector Rev 4(1):3–18
28. Lettieri E, Masella C (2009) Priority setting for technology adoption at a hospital level: relevant issues from the literature. Health Policy 90:81–88
29. Teplensky JD, Pauly MV, Kimberly JR, Hillman AL, Schwartz JS (1995) Hospital adoption of medical technology: an empirical test of alternative models. Health Serv Res 30(3):437–465
30. Gagnon MP (2014) Hospital-Based health technology assessment: developments to date. Pharmaco Econ 32:819–824
31. Foglia E, Lettieri E, Ferrario E, Porazzi E, Garagiola E, Pagani R, Bonfanti M, Lazzarotti V, Manzini R, Masella C, Croce D (2017) Technology assessment in hospitals: lessons learned from an empirical experiment. Int J Technol Assess Health Care 33:2
32. Lettieri E, Masella C, Nocco U (2008) Budgeting and health technology assessment: first evidence obtained from proposal forms used to submit the adoption of new technology. Int J Technol Assess Health Care 24(4):502–510
33. Davis FD (1985) A technology acceptance model for empirically testing new end-user information systems: theory and results. Ph.D. thesis, Massachusetts Institute of Technology, MA, USA, 20 Dec 1985
34. Davis FD (1989) Perceived usefulness, perceived ease of use, and user acceptance of information technology. MIS Q 13:319–340
35. Venkatesh V, Morris MG, Davis GB, Davis FD (2003) User acceptance of information technology: toward a unified view. MIS Q 27:425–478
36. Venkatesh V, Davis FD (2000) A theoretical extension of the technology acceptance model: four longitudinal field studies. Manag Sci 46:186–204
37. Gastaldi L, Radaelli G, Lettieri E, Luzzini D, Corso M (2019) Professionals' use of ICT in hospitals: the interplay between institutional and rational factors. Int J Technol Manag 80 (1/2):85
38. De Benedictis A, Lettieri E, Gastaldi L, Masella C, Urgu A, Tartaglini D (2020) Electronic medical records implementation in hospital: An empirical investigation of individual and organizational determinants. PLoS One 15(6):e0234108
39. Iadanza E, Gonnelli V, Satta F, Gherardelli M (2019) Evidence-based medical equipment management: a convenient implementation. Med Biol Eng Comput 57:2215–2230

Chapter 10
Reimbursement Systems for Healthcare: Considerations on "Pay for Performance"

Claudia Vienken, Emanuele Gatti, and Joerg Vienken

Abstract Demographic changes, limited healthcare budgets and performance-based attitudes for medical therapies have led to Pay-for-performance programs in healthcare. Here, consumer (patient), provider (physicians and nursing staff) and payer (patient and health insurance funds) are all involved. To reach targets based on measurable quality indicators, incentives are provided for the efficient use of medical resources and medical devices. The establishment of such key factors needs a consensus among the involved stakeholders to be successful. This consensus can only be reached if the interests of these groups are balanced, beard in mind and special attention is paid to such a complex process. Artificial intelligence-based analyses of large patient databases may be of help in improving this situation. Medical devices underwent a metamorphosis from a simple instrument to a complex tool allowing for sophisticated performances and the active, online interaction with treatment modalities. Innovative devices allow for covering preventively responsibilities in medical care and impact disease management. Vertically structured companies can serve as a model for successful corporates in medical device technology.

Introduction

Public expenditures for health care reach on average the total of 9% of GDP in most industrialized countries according to the Organization for Economic Cooperation and Development (OECD). There is a clear positive association between healthcare spending per capita and life expectancy. Depending on risk factors, countries with

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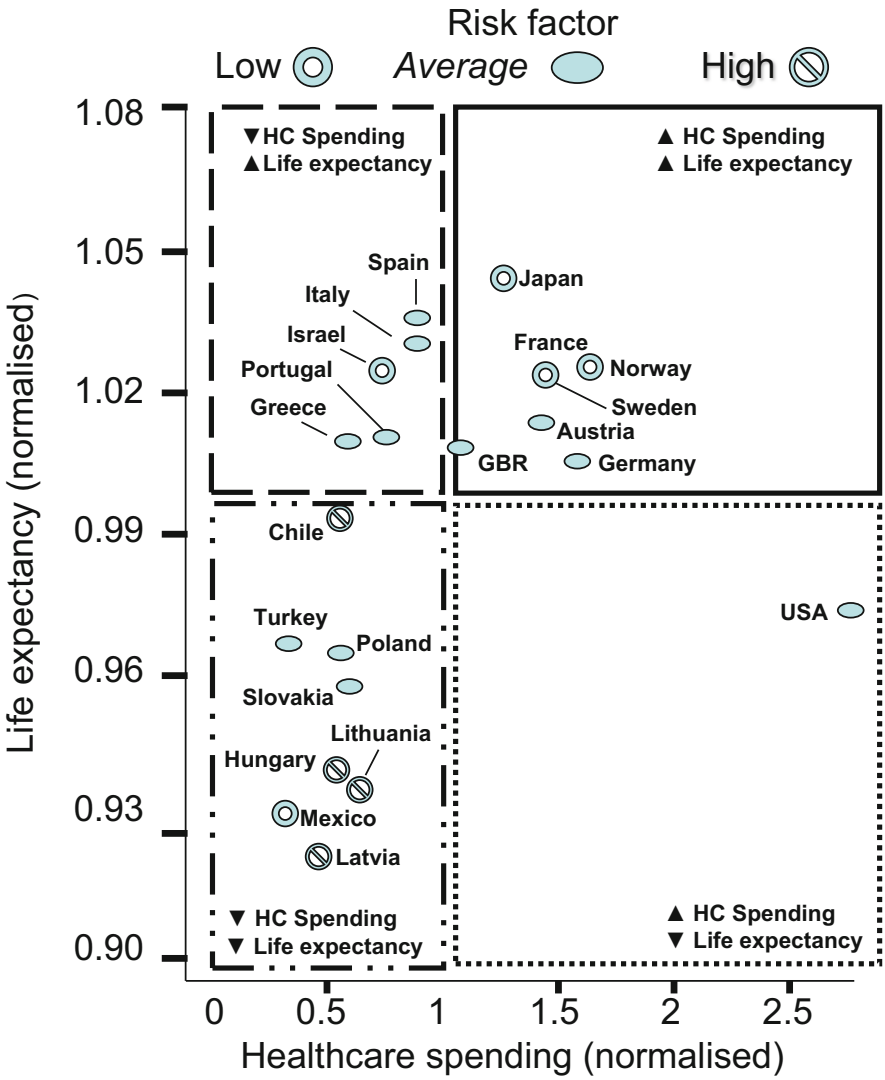

Fig. 10.1 Health care spending, life expectancy (arbitrary units) and risk factors in different countries. There are countries with low healthcare expenditure (upper left-hand panel) but with increased life expectancy. Compared to other countries, the USA (lower right-hand panel) exhibit a moderately reduced life expectancy despite high expenditures on healthcare. (Adapted from [1], *GBR* Great Britain)

the highest health care expenditures (HC spent) however, do not automatically show the best results in this realm (Fig. 10.1, [1]).

As shown in Fig. 10.1, there are still improvement opportunities in both healthcare efficiency and healthcare expenditure. Currently observed changes in

demography have a strong influence on both factors. An increased number of elderly people will depend on a more intensive care and thus create higher levels of related cost. Further, the development of both, high-cost medical devices, therapies and pharmaceutical agents for individualised therapies imposes already to date a high pressure on healthcare budgets. Consequently, the search for measures to increase both, efficiency and performance, as well as the identification of related guiding factors have become a matter of debate since many years [2–4].

In addition, recognising the growing prevalence of value-based care, medical device companies are increasingly incorporating risk-sharing programs into their customer agreements. Conceptually, these efforts are a step towards aligning medical device suppliers and hospitals to providing value-based care. In the context of shrinking margins and the striving for a concept towards value-based care, risk- and budget-sharing contracts with medical device manufacturers and other healthcare stakeholders hold significant promise for healthcare systems. This affects all stakeholders, if they are fully informed about related financial consequences before entering these arrangements. Mutually accepted quality indicators are a *sine-qua-non* condition when considering value and risk in healthcare.

10.1 Pay-for Performance and Clinical Therapies

Hospitals measure the patient's length-of-stay and many use this measure as a surrogate marker for quality and efficiency. Questions arise whether this first metric is also considered by patients when thinking about hospital quality. Even from an administrative point of view, the financial benefit of a patient's reduced length of stay cannot be realised, unless cost of labour is reduced at the same time.

At the onset of the 1960s, such debates have been advanced and investigations have been performed about "Pay-for-performance (P4P)" programs in the United Kingdom (UK) [5] followed by the USA in the later 1990s [6]. They circulated around efficient and high-quality healthcare systems, because published data have revealed inefficiencies in the British healthcare system [7]. Central questions arose already at that time on how to define key figures for assessing performance, quality and efficiency in order to find a measure for an adequate payment [4]. Given that such figures are identified, improvements in the status-quo of healthcare systems are possibly realized both in a timely and long-term manner [8]. A general approach to get an understanding of "performance" in this chapter and defining value in healthcare can be taken by:

$$\text{Value} = \frac{\text{Quality of Care} + \text{Services}}{\text{Cost}}$$

where "Cost" combines medical cost and nonmedical cost. Medical costs comprise both therapy and hospitalisation cost, medication, outpatient care and patient-

transportation, whereas nonmedical cost refer to productivity losses of patients and caregivers, as well as cost related to environmental burdens.

Improving Quality of Care, especially for patients with chronic diseases, is generally realized by financial and nonfinancial incentives for physicians and care givers. Today, healthcare providers and payers spend substantial resources collecting, analysing and reporting data on providers' performance. Associated negative aspects and undesirable consequences have to be minimized by optimising such incentives in the long run.

Based on experiences in the UK, many countries have recently started with "Pay-for-performance (P4P)" programs in healthcare, mostly for the management and therapies of chronic diseases, such as e.g. diabetes [9, 10]. They focus on both, quality of care and quality of life (QoL) in affected patients [8]. Still to date however, many of the P4P programs lack long-term experience and thus, contradictory and non-reproducible results are still common [11].

10.1.1 Pay-for-Performance (P4P) Programs

Pay-for-performance (P4P) programs in healthcare are based on control mechanisms which allow for the quality improvement of medical therapies whilst strictly coping with current limited healthcare budgets. Patients and healthcare providers further determine boundary conditions which are set by both, the general health situation of a defined population, and by a currently diminished availability of care givers. For instance, on the one hand, the patients' performance depends on their individual health behaviour including risks, such as a high body mass index, the deliberate exposure to infection or underlying noncommunicable diseases. On the other hand, healthcare providers face general healthcare problems, such as demographic changes or the impact of policy decisions. All stakeholders must cope with mutual benefits, claims and payments, whilst all parameters depend on healthcare resources, available expenditures and funding (Fig. 10.2).

In addition, adequate allowances for physicians and caring staff should positively contribute to quality of life (QoL) and a healthy and productive ageing of patients. A performance- and quality-based reimbursement system for ambulant- or hospital-based therapies, a so-called P4P program aims at providing solutions and a way-out from budget constraints in healthcare. P4P is currently advanced by two different models:

1. **Prospective model**:
   Bonus payment for achieved performances in advance.
2. **Retrospective model**:
   Reimbursement of performance depending on the assessment and analysis of preassigned key factors.

Both models depend on targets and key figures which may change according to actual boundary conditions. Consequently, "P4P is not a magic bullet" as it was

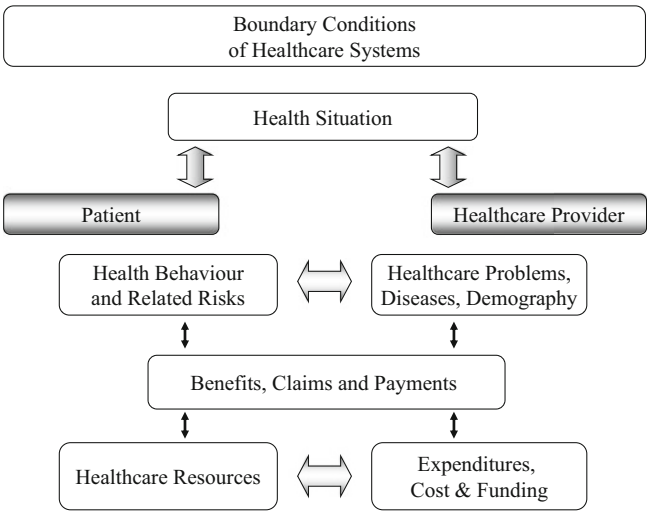

Fig. 10.2 Interdependencies of patients and healthcare providers in terms of mutual benefits, claims and payments (own representation).

explained by M. Roland [12]. P4P systems need to be strategically and continuously adapted to the stakeholders' actual needs to sustain improvements in the quality of care in the long run.

The general premise of P4P is based on the assumption that physicians in charge will react positively on financial and nonfinancial incentives and can thus be motivated to improve their performance and to successfully reach predetermined targets [13]. However, and unfortunately, a convincing general proof of efficiency shown by existing P4P models cannot yet be demonstrated [6, 11, 14]. Possible reasons are incentive systems which depend on location and type of hospital, limited healthcare budgets and increasing material and labor cost, as well as problems in defining and assessing therapy quality. Overall, it must be assumed that special local overall conditions exacerbate the identification of key indicators for clinical efficiency [6, 11].

10.1.2 Determining Factors for the Introduction of P4P Programs

Boundary conditions for P4P models are highly relevant for the development of P4P systems. Before introducing P4P programs, determining bystander conditions have to be identified, defined and modelled at an early stage. These factors include the type and organisation of national healthcare systems and the amount of available

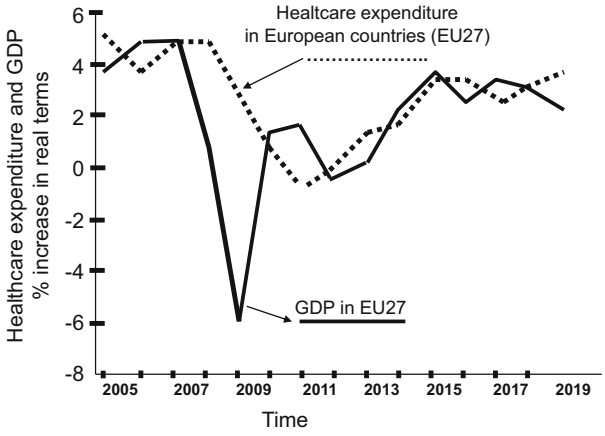

Fig. 10.3 Percent changes in annual healthcare expenditure and gross domestic product (GDP) in real terms. (Adapted from [15])

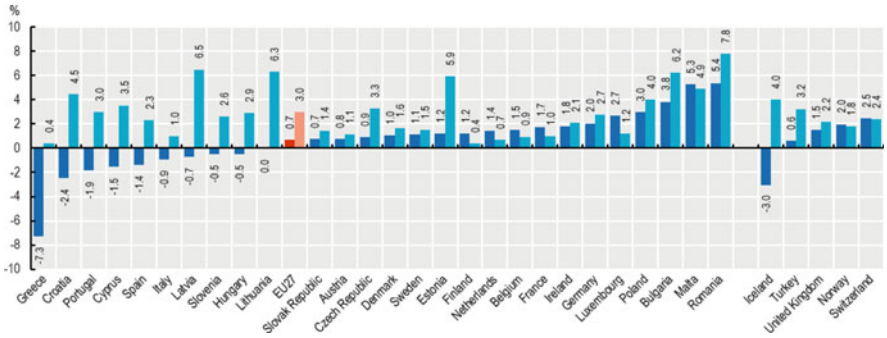

Fig. 10.4 Percent growth rates in expenditures for healthcare *per capita* in European countries (2008–2013 dark blue bars) and 2013–2019, bright blue bars). All European countries show an increase of health expenditure between 2013 and 2019. An average of 3% increase is found for the EU27 in this period. (Adapted from [15])

healthcare budgets, the number of affected patients and their age distribution in related areas.

In European countries (EU27), healthcare budgets in comparison to the GDP have reached a plateau in recent years (Fig. 10.3).

It is noteworthy that healthcare expenditures computed per capita have increased as well (Fig. 10.4, [15]). Reasons for this notion are changing demographic factors, i.e. an increasing number of elderly people, an improved healthcare availability and the use of perfected and possibly expensive medical devices. Data from Germany support the notion that the number of elderly people is currently rising [16]. The number of people with advanced age (80 years and more) increased by 4.5%

between 2011 and 2020 and reached 5.9 million (7.09% of the total population [17]). Actual forecasts guestimate an even higher figure in this cohort for the next decades. When the birthrate will reach a level below the so-called "compensatory level", problems in per capita healthcare budgets will become even more pronounced. The "compensatory level" refers to a birthrate which is necessary to maintain the actual population number. When birthrates drop and the number of elderly people increases, healthcare cost per capita cannot be covered by the younger generation in the future. It is, therefore, reasonable to ask whether P4P models as a preventive action can help to overcome these problems.

10.1.3 Motivation of Involved Stakeholders and Their Possible Conflict of Interest

It is generally assumed that performance-based allowances can contribute both to an improved healthcare quality whilst keeping cost under control. The success of P4P models however, depend on how early possible conflicts of interest between the involved stakeholders are identified and qualified. Unfortunately, a general consensus between the different stakeholders in healthcare provision does not exist yet. A common understanding is mandatory of why and how quality indicators of a therapy success are applied. Only hereunder acceptance of all stakeholders can be guaranteed despite certainly existing different conflicts of interest [17].

In the following, we provide an overview of those stakeholders who determine the success of a P4P program.

Patients as Stakeholders

Patients are to date better informed and seek validation and guidance during therapies. They demand the provision of adequate healthcare technology, have a close look on process quality during treatment and expect treatment experience and personal involvement by caregivers. Consequently, patients enjoy top priority in all P4P programs. These programs start from the premise that the patient's QoL will be improved if more efficient medical devices are used and therapies are provided more closely in time. However, the success of a therapy depends on both the subjective feeling of a patient in terms of e.g. perceived quality of treatment, her/his mental health and her/his initial clinical situation. In addition, patients link "quality" not only to an outstanding clinical treatment but also to both a sympathetic attention of nursing staff and explanatory communication skills of physicians in charge [17]. Such skills impact patient compliance and therefore determine the positive treatment outcome.

The mutual cooperation of patients with the respective doctor and thus their compliance depends on socioeconomic aspects, i.e. their individual medical records

combined with their private cost sharing. In healthcare systems without statutory health insurances, cost sharing is high and the impact of patient compliance is more pronounced. Further, patients have often only limited or asymmetric knowledge and information about necessary therapies, such that they are unable to judge the need of a medical therapy, the application of a costly medical device and its best achievable result. Consequently, an active cooperation and a transparent communication between physicians and patients are necessary conditions for metrics to improve clinical quality and performance.

Physicians as Stakeholders

Physicians represent the executive body in P4P programs. Defined medical outcomes are determined by the physicians' performance which is, therefore, addressed by P4P allowances. Typical P4P programs provide additional remunerations given that medical records improve in a defined period of time. Physicians, who participate in P4P programs, are prone to achieve good therapeutic results through efficient treatment modes and best-performing medical devices [17]. In this context, a conflict of interest between patients and physicians cannot be excluded. Patient welfare can turn out to be even subordinated, if high financial incentives are provided for applying specific treatment options. In contrast, the social and personal reputation of a physician is recognised by premium-quality of care and is last-but-not least determined by medical ethos. P4P programs, however, may also have a negative impact. For instance, British physicians were afraid to lose their autonomy and their professionality after the introduction of P4P programs. They argued that the nursing staff will be responsible for their medical activities due to cost and time constraints [5].

P4P programs are no stand-alone systems. They allow to compare the efficiency of physicians, outpatient centres and hospitals. When documented, patients might be willing to change the doctor in charge due to their respective delivered performance, which finally motivates the doctor to improve his personal performance.

Hospital Management as a Stakeholder

The hospital management is assigned to coordinate P4P programs and is in charge to identify organisational tools and modalities to reach predetermined P4P targets. The success of these activities depends on whether targets are mutually accepted by the clinical stakeholders, whether performance indicators are reasonable and how existing therapy standards can be modified [7].

The hospital management obviously has to focus first on patient satisfaction and both therapy performance and success, not neglecting the access to healthcare provision [7]. These aspects also determine the incentive commitment for physicians, which should motivate physicians to improve their performance.

The primary goal of the hospital management is focused on increasing cost-efficiency. By improving therapy quality and optimising medical device resources, medical malpractice should be minimised which finally should lead to a reduced hospitalisation.

Health Insurance Funds as Stakeholders

Health insurance funds top the hierarchy of P4P programs. They define the targets in healthcare to be reached by the stakeholders involved. In addition, they settle financial means necessary to reach the appropriate targets. Under the control of health insurance funds, treatment costs are determined by available healthcare budgets, which finally predefine quality and orientation and targets of health services. The basic interest of this stakeholder is to provide appropriate medical benefits with high efficiency at minor cost. When introducing P4P programs, health insurance funds further expect to reduce cost related to over- and under supply of prescribed medical devices, as well as to inappropriate healthcare. The establishment of healthcare standards could help in this regard.

It must be mentioned however, that health insurance funds—as a disadvantage—have to bear in mind and prioritise the interests of several principal actors.

10.1.4 Case Report: The P4P System in the United Kingdom

A few decades ago, there was little effort to assess the performance of healthcare systems due to a general agreement that healthcare quality and medical treatment was unmeasurable. Therefore, no agreement among the involved stakeholders could be simultaneously reached about the nature and dimension of "quality indicators". Today, healthcare providers spend substantial resources collecting, analysing and reporting data on providers' performance and link their efficiency to variable incentives [4]. In 2004, the United Kingdom introduced one of the World's largest Pay-for-performance programs, the "Quality and Outcomes Framework (QOF)". Within this framework, data on medical expenditures and medical personal were recorded in relation to the income of family doctors and special hospitals for patients with chronic diseases were established. The British Government provided additional funds of 1.8 billion £ over 3 years and by this means increased the income of family doctors by 25% as an incentive for a better therapy quality [18].

Already in the beginning of realising the P4P programs, it became clear that P4P models are highly suitable for the documentation of successful therapies in chronic diseases. For instance, pharma-, research- and medical opinion leaders agree upon saying that chronic kidney patients and the treatment of haemodialysis are keys to innovative concepts of care [19].

The following actions have been taken in the UK in 2004:

1. Establishment of a set of quality indicators consisting of 147 key figures from four different quality domains, such as clinical processes and structure, patient outcome and patient satisfaction.
2. Round-up of key figures to a maximum of 1000 points in order to determine a final score for the determination of payments.
3. Payment of 120 £ per achieved point.
4. Establishment of "exception-rules" as a risk adjustment. Due to administrative or specific medical reasons the therapy of patients, who deny a therapy or suffer from actually occurring additional diseases, can be excluded from the quality indicator benchmark.
5. Application of "Electronic medical record systems (EMR)" to document medical interventions and to identify medical therapy improvements.
6. Annual readjustment of QOF by the British Medical Association and the Department of Health.

10.1.5 Results: General Observations

The P4P program realised in the UK in the last decades concentrated on the prevention and treatment of chronic diseases due to a given simplified control of impacting parameters. Since the introduction of the QOF, verifiable improvements were seen in the British healthcare service. However, a precisely controlled definition of quality indicators and a closely controlled analysis of type and delivery of incentives render a clear-cut conclusion about advantages or even disadvantages difficult. As a program, which was endowed by the British Government, subsidiaries were limited in time and did not finally yield general structural changes. Despite additional bonus payments for physicians, hospital administrations had to make substantial investments into data recording systems in order to reach quality targets. This was a handicap especially for low-performers in the P4P program.

It can be assumed as an outlook, however, that the enormous actual increase in data storage capacity, combined with intelligent analytical tools, the evaluation of patient data will allow for a better targeting of aims and goals in future P4P programs. Indeed, a significant rise in patient data is also linked to newly available noninvasive sensors for physiological parameters. They will allow for a closely linked scalability of incentives for both hospital administrations, nursing staff and physicians. Future P4P programs also have to take data-protection and -anonymisation into account, which makes it difficult to obtain a reliable assignment of achievements to one or the other stakeholder.

10.1.6 Results: Improvements in Clinical Quality Indicators

The introduction of P4P programs in line with the Quality and Outcomes Framework (QOF) has led to substantial clinical benefits. When looking at specific diseases, such as diabetes, pneumonia, asthma and coronary heart disease, quality scores rose continuously [5, 14]. For the endpoint “mortality” however, no significant differences could be observed when comparing control regions with a verum group in North Western UK (Fig. 10.5, [14]).

10.1.7 Lessons Learned from QOF Daily Practice

Key elements for the improvement of medical treatment need to be those quality indicators which allow for an objective and reliable assessment. Those indicators are both, multifactorial and multidimensional and are characterised by the following criteria [17]:

1. **Validity** criteria have to be determined by a committee of experts.
2. **Sensibility** and reactivity for changes and modifications.
3. **Reproducibility** under multiple medical conditions.
4. **Acceptance** by all stakeholders.
5. **Measurability** even for different disease states.

Lessons learned during the introduction of QOF, show that management structures, workflow processes and patient outcomes impact key quality figures to a high degree [20]. **Structural parameters** take into account the value of staff qualification and material resources. They are directly linked to the availability and performance of medical devices. Strategies for the improvement of high-value care depend on how these resources are available and efficiently used. **Workflow indicators** allow for documenting patient data and related information as well as details on the

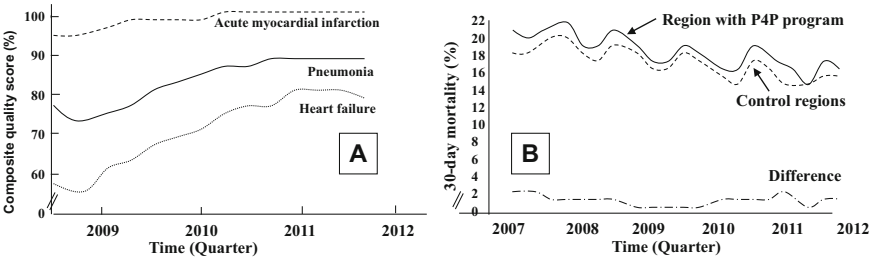

Fig. 10.5 Average hospital performance on quality scores for three clinical conditions linked to incentives in a P4P program in UK (**a**) and paralleled in hospital mortality at 30 days (**b**). Whilst hospital performance improves over 4 years, no difference can be found between regions exposed to a P4P program and control regions for %-mortality under the same conditions. (Adapted from [14])

performance of individual clinical treatments and prescriptions for medicinal drugs [17]. For instance, in QOF the number of patients is covered by workflow indicators, who have been treated by defined clinical guidelines. It is possible to easily and continuously measure workflow indicators. They are, therefore excellent P4P indicators, as they also allow for the precise information on the performance of physicians in charge. Finally, data on **patient outcome** determine to a high degree whether a treatment was successful. Data on patient outcome can be defined by the following 5 D's [21]:

- **D**eath. Despite a defined treatment, death cannot be avoided.
- **D**isease. Symptoms and clinical sequelae can still not be avoided.
- **D**iscomfort. There is still a number of adverse reactions, such as pain.
- **D**isability. The treatment leads to an impairment of body functions.
- **D**issatisfaction. Patients still suffer from a therapy and show personal discontent.

The success of a treatment needs to be qualified by both, the judgement of the doctor in charge and the subjective perception of the patient. This correlation has proven to be important. Perceptions on the patient's QoL strongly depend on her/his actual health condition and the capability to cope with her/his individual situation. For instance, two patients with the same degree of sickness can still show different sensations of their QoL [22].

As a conclusion, no supporting observations and evidence can be reported that hospitals, whilst having operated under P4P programs for a longer period of time, had a lower patient mortality than other hospitals. This suggests that even under an increased observation time, it is unlikely that under the current conditions P4P programs will turn out to be successful in the future [6].

Future schemes for improving healthcare need to focus especially on the elderly population with its deteriorating physiological conditions, because the subsequent risk to develop chronic diseases leads to an increased care dependency. Prevention measures should be included in scores to describe healthcare performance as additional quality markers [23].

Further, an iterative approach in terms of *design thinking* for the creation of value should be initiated and is recommended. With *design thinking* solutions can be obtained for a better understanding of the position and needs of users (physicians, caregivers, patients and other providers), and assumptions for a better performance and routes to redefine value in healthcare can be elicited. *Design thinking* approaches in healthcare are able to enhance innovation, efficiency, and effectiveness [24].

10.2 Performance and Compensations for Medical Devices

Pay-for-performance programs have neglected the role of medical devices and their specific contribution to treatment quality. The question arises, whether a special focus on device performance or on innovative device features may contribute to healthcare quality and thus to its value. In the following, we will discuss recent

trends and changes in the medical device market and identify the new role of medical device manufacturers.

10.2.1 Trends and Observations in the Global Medical Device Market

Health and healthcare are influenced by many key factors, such as *patient medication* and *nutrition, cosmetics* and *treatments with medical devices*. Further, medical devices are not exclusively applied in ambulant and clinical therapies. They also play a significant role in in vitro diagnostic analyses and are therefore addressed by a recently issued EU regulation the "IVDR in vitro diagnostic medical device regulation" [25]. The IVDR parallels the new EU medical device regulation (MDR [26]) and was also issued on May 26, 2017. In contrast to the MDR, which became effective on May 26, 2021, the official date for its starting validity is May 26, 2022.

Therapies with medical devices are directly linked to quality and outcome of patient care and thus, determine QoL. The portfolio of medical devices also includes healthcare budgets and profitability for medical device manufacturers (Fig. 10.6).

Medical devices can be considered the motor in many therapeutical interventions. In order to be innovative and cost efficient, developments in medical technology undergo a long-lasting process from concept, production and approval to marketing and clinical application. By collaborative interactions and commitments between the many involved stakeholders, priority needs within regulated areas and points of intersections have to be defined to address benefits. *Design thinking* approaches start here and could support the enhancement of innovation, efficiency and reliability in medical device technology [24]. From a manufacturer's point of view, the three "G's" play a major role, and have to be practiced:

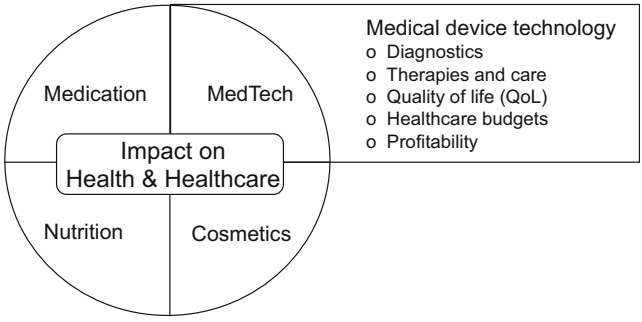

Fig. 10.6 Health and healthcare are influenced by many key players, such as medication, nutrition, cosmetics and treatments with medical devices. Apart from direct interactions with patients in terms of diagnostics, therapies and QoL, the portfolio of medical devices also impacts healthcare budgets for health insurance funds and the profitability of manufacturers

- **G**ood Manufacturing Practice (GMP),
- **G**ood Laboratory practice (GLP) and
- **G**ood Clinical Practice (GCP).

See also Chap. 13 for details on GMP, GLP and GCP. In addition, medical devices can only be marketed when they have been approved by authorities, such as e.g. EMA (Europe), FDA (USA) or MHW (Japan) after having undergone successful clinical trials from Phase I to IV. It is understandable that these processes need time and money.

As compared to clinical therapies and related P4P programs, two aspects determine investment and innovation in the medical device field: Compliance and Cost.

Compliance refers to established standards and regulations, such as e.g. the EU Medical Device Regulation MDR (which came into force on May 26, 2021, [26]), the in vitro Diagnostics Regulation (MDR/IVDR [25]), the ISO 10993 (Biological evaluation of medical devices), the ISO 14971 (Application of risk management to medical devices [27]), and Regulation (EC) 1394/2007 on Advanced Therapy Medicinal Products (ATMPs [28]) or others. Most of them are touched in detail in Chaps. 4, 5 and 13.

Cost and investments for research, production and marketing determine competitiveness of medical device manufacturers in a global market. Both terms, compliance and cost, are addressed in two statements with a similar sentence construction.

Already in 1957, Mary Lasker (1900–1994), an American healthcare activist and founder of the "Lasker-Award for Medical Research and Technology", commented concerns about necessary high cost for investments in innovative medicines [29]:

If you think research is expensive, try disease!

Thinking in a similar way, the former U.S. Deputy Attorney General Paul McNulty addressed compliance in 2009 [30]:

If you think compliance is expensive, try non-compliance!

International regulatory affairs, as well as prescriptions to perform quality- and risk-management processes, are costly and affect economic growth and the competitive position of medical device manufacturers. The return-on-investment (ROI) of globally active medical device producers further depends on national regulations, incentives and subventions for medical devices and related therapies and are thus, uncontrollable by a manufacturer. As shown e.g. for the treatment of chronic kidney failure, the reimbursement of thrice-weekly haemodialysis, including cost for medical devices, strongly depends on national variables (Table 10.1, [31]).

Budgets in healthcare depend on their availability. Current global trends tend to budget restrictions despite the increase in the number of patients in need. However, some financial resources for healthcare and medical devices are still for things without value. Analyses from the USA attest that a high amount of money and budgets in healthcare are spend on nothing due to system failures (Table 10.2, [32, 33]. The authors of these analyses, W. Shrank and colleagues, also reviewed the available literature on efforts to reduce wasted money and concluded that about

Table 10.1 Reimbursement per thrice-weekly haemodialysis services in different countries (in US-$)

	Belgium	Germany	The Netherlands	United Kingdom	France	US–Ontario	Canada
Self-care haemodialysis	1045	675	1668	744	909	689	502
Home haemodialysis	1045	675	1246/1905	744	816	689	385
CAPD	985	1077	1126	502	718	689	636
APD	985	1077	1126	612	925	689	733
Hospital haemodialysis	1608	675–1131	1668	744	1364	689	745

Data taken and compiled from [31], CAPD - Continuous Ambulatory Peritoneal Dialysis, APD - Automated Peritoneal Dialysis

Table 10.2 Identified six domains showing a high range of wasted annual money in healthcare in the United States of America.

Wasted money [in billion US $]	Reason	Value of savings from interventions [in billion US $]
104.2–165.7	Failure of care delivery	44.4–93.3
27.2–78.2	Failure of care coordination	29.6–38.2
75.7–101.2	Overtreatment or low value of care	12.8–28.6
230.7–240.5	Failure of pricing	81.4–91.2
58.5–83.9	Fraud or abuse	22.8–30.8
265.6	Administration complexity	n.a.
760–935	Annual cost of waste (25% of total US healthcare spending)	
	Savings from interventions	191–282

Data compiled from [33], *n.a.* not assessed

25% of these expenditures could be reduced with the implementation of well documented current programs. According to an analysis of the US Institute of Medicine interventions, which have proven to be of value in healthcare, such programs need unfortunately 15–17 years until they penetrate general use in the healthcare environment. Whether these figures from the USA are representative for other countries either, still remains a matter of debate.

The question arises on how these cost considerations can be put into positive perspectives and how financial and hardware resources for medical devices can be exploited more efficiently. The look on general conditions of medical device- and healthcare providers and related markets may offer a closer understanding of the current situation (Fig. 10.7).

The medical device market has become global. The export of devices and related systems determines production, marketing and sales and last but not least also foreign investments. Manufacturers profit from practical clinical applications of

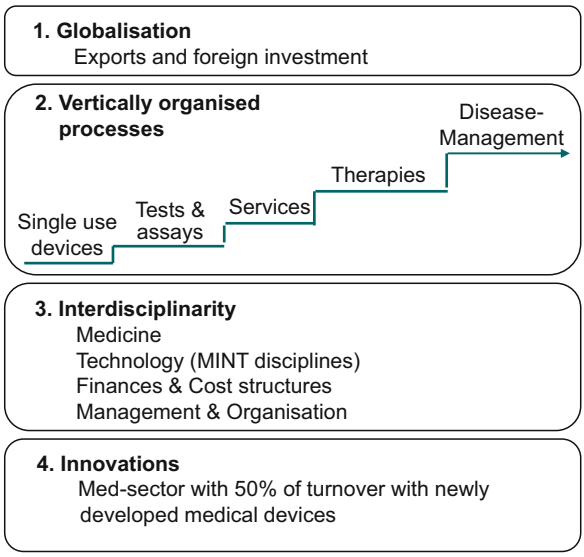

Fig. 10.7 Current situation and boundary conditions of modern medical device industries

medical devices based on intense scientific investigations, which are performed both in-house and in collaboration with academic institutions. As a consequence, the production of medical devices is subject to a "systems approach", which includes vertically organised processes from in-house production to extramural clinical application. Cost considerations and performance assessments are key figures here. For instance, concepts to abandon reuse of devices and supply instead single use items have been advanced in order to achieve safety and guarantee performance during the device's shelf-life time. The use of reliable in vitro test systems to guarantee high device quality prior to clinical application, the involvement of devices into the delivery of services and their application in both ambulant and clinical therapies under the supervision of a disease management represent further steps in such vertically organised processes (Fig. 10.7).

The medical device industry further needs employees with an interdisciplinary background. Medical devices, once developed, cannot be further developed and sold like commodity products. Only employees with curiosity and knowledge in scientific disciplines, such as natural sciences, engineering, finances and—not to forget—ethics are a *conditio-sine-qua-non* for successful innovations and subsequent success in healthcare. The huge number of 10,480 granted European patents in 2020 [34] provides evidence that MedTech has become one of the most successful engineering realms.

The performance of medical devices during therapeutical interventions and diagnoses depends on heterogeneous clinical targets. In other words, a "one-fits-all" device does not exist. For instance, an integrated performance of different functionalities of medical devices will be necessary, given that the expected increasing use of telehealth technology will come true (Fig. 10.8). Sensors for physiological

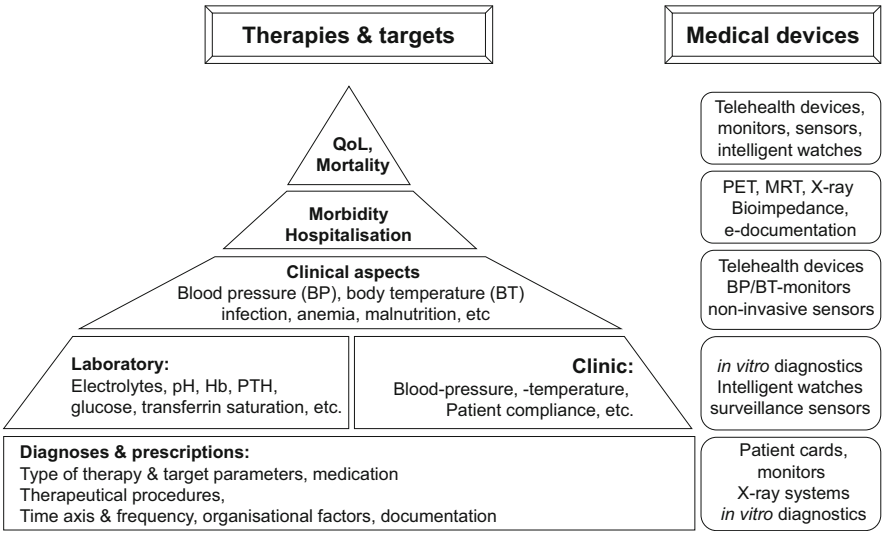

Fig. 10.8 Scheme of therapeutical and analytical interventions in healthcare services supplemented by some examples of related medical devices. Based on the expected increasing use of integrated performance of medical devices, telehealth allows for new device opportunities in terms of a systems approach

parameters, both invasive and noninvasive, combined with broadcasting- and documentation-systems are models for such a systems approach in Medical Technology.

It's not surprising, that the required performances and needs for quality and reproducibility of medical devices (MDs) has led to the availability of more than 400,000 different types of medical devices and in vitro diagnostics on the European Market in 2017 [35]. A general scheme for the use of MD's aims, targets and types of devices is shown in Fig. 10.8. In addition, the need for sophisticated complex medical devices expands, when medical knowledge increases and clinical interventions are performed under conditions of evidence-based medicine. Taken together, the medical device industry is exposed to big challenges, not to keep only their shareholders satisfied. These challenges can be described by the following five "P's":

- **P**roduct: A MD should be marketable in global markets.
- **P**otential: A MD should be able to be used synergistically with other MDs.
- **P**erformance: A MD should perform well under all environmental conditions.
- **P**rofit: A MD should allow for a considerable return-on investment (ROI).
- **P**erspectives: A MD should also allow for establishing a platform technology.

10.2.2 Innovative Products for the Reduction of Total Cost of Care

An ideal example to prove the potential of innovative medical devices can be taken from haemodialysis (HD), a therapy for the treatment of chronic kidney patients. It is based on an extracorporeal blood circuit which allows for purifying blood from uremic retention solutes. Patients suffering from end-stage kidney disease have to undergo an HD-therapy three times a week for the rest of their lives, if no organ transplant is available as an alternative. In 2019, a global number of 4,370,000 patients suffer from end-stage kidney disease (ESRD), 3,160,000 thereof are treated by haemodialysis, 393,000 by peritoneal dialysis and 817,000 have received a kidney graft [36]. Medical devices used for HD are usually composed of disposable syringes, tubing, filters and sensors. With the help of dialysis machines (monitors), the treatment is realised and continuously controlled. Treatment parameters are automatically documented with the help of a software which is part of the dialysis monitor and stored on a patient card. This enables nephrologists to compare treatment performances between two dialyses of an individual patient or even between different patients.

In order to guarantee safety and security against infections and cross contaminations with viruses between neighbouring patients in a dialysis centre, single use devices have been preferred compared to reused devices. Haemodialysis represents a chronic therapy with a repeated thrice-weekly use of medical devices for many years. Given that the global 3,1 million HD-patients are treated with single use devices, a weekly supply of around 10 million sets (syringes, tubing, filters) is needed. Therefore, the timely supply, reproducible performance and quality of these devices must always be under control and the clinical success of treatments be followed.

Therapy providers or physicians, who run dialysis centres, are responsible for disease management, which includes responsibilities for the individual therapy, for devices and their actual performance as well as for the availability of a functioning medical device item (Fig. 10.9a).

The average cost for haemodialysis treatments in the Western hemisphere adds up to about >65,000 € per patient and year and are to be covered by health insurance funds or healthcare budgets. However, many countries without health insurance exist, such that kidney patients remain untreated. Initiatives are currently underway to achieve cost reduction by establishing a close control of both medical device performance and treatment efficiency (Fig. 10.9b).

With innovative medical devices in haemodialysis, therapy control and responsibility can be delegated to and adopted (at least in part) by medical devices. Noninvasive sensors (with focus on "noninvasive") for blood temperature [37], blood volume [38] and body composition (water, fat, muscle mass) [39, 40], pulse-rate, pulse wave velocity [41], online clearance measurement of filters [42], closed loop lung ventilation [43], glucose analyses [44] and others, are capable to continuously assess and control physiological parameters of a patient. When applied as a closed loop and linked to the dialysis monitor, treatment conditions can be acutely modified and adapted depending on the patient's performance.

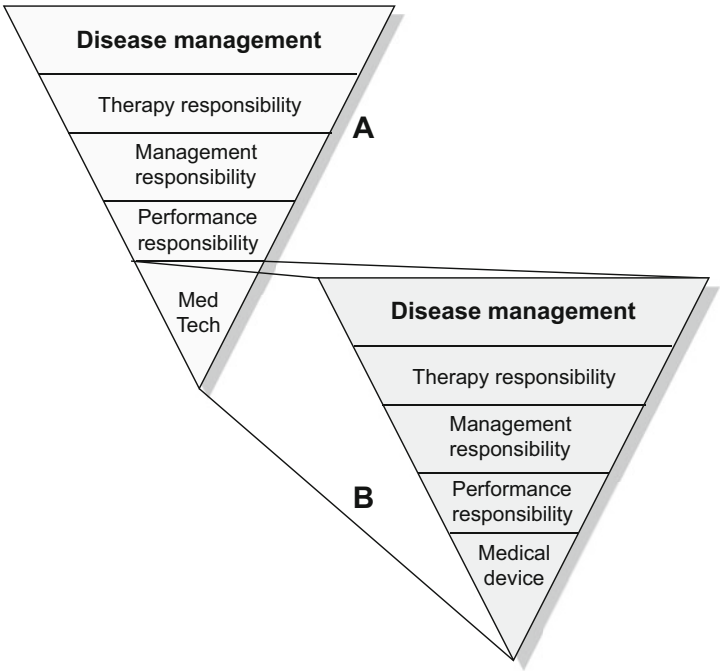

Fig. 10.9 Therapy providers or physicians, who run dialysis centres, are responsible for disease management. It includes responsibilities for the individual therapy, for the correct use of sterile medical devices and their actual performance, not to forget the availability of functioning therapy systems (**a**). With innovative medical devices, therapy control and responsibility in haemodialysis can be delegated to and adopted (at least in part) by medical devices (**b**). Cost savings are supposed to be realised then

Data and figures obtained by these feedback controls are currently collected and incorporated in global big data banks [45]. They allow for detailed analyses of different patient cohorts, their clinical performance and QoL. As a result, therapies can be adapted to an acutely changing patient condition and treatment modes optimised. With the help of this device technology and the future combination with tools of artificial intelligence a continuous monitoring of long-term patient behaviour and treatment quality can be achieved, disease management technically realised and last-but-not least cost of care reduced (Fig. 10.9b).

10.2.3 Adaptation to Different Requirements of International Healthcare Systems by Innovative Processes

Four out of five MedTech companies have either changed their business model in the past 3 years or are currently considering changing it. Reasons for this observation are changes in macrotrends, such as

- Cuts in healthcare spending
- Decline of investments on prevention of disease
- Focus on patient-centric approaches
- Value *vs*. volume considerations

How to cope with these findings and still provide a profitable business for Healthcare Provider Organisations (HPOs)? Budgets of healthcare systems may suffer from wasted resources. Obviously professional managerial skills are needed to improve the exploitation of financial resources. One solution might be to reduce the number of involved stakeholders and keep responsibility and management of resources for healthcare in one hand or in one company. This leads to the foundation of *vertically structured* companies, who control the entire business-to-consumer chain. The realm of haemodialysis offers such opportunities, when a company provides goods and services for patients and is simultaneously able to run dialysis clinics and centres. A considerable asset of such companies is based on applied research on polymers and on instruments for dialytic therapies, the production of medical devices and their adaptation to medical needs through the realisation of clinical trials. By this means, clinically derived documents can be timely submitted for approval processes and investigations on specificities of global markets can be performed in-house. Manufacturing all necessary products for dialysis therapy in one hand and running dialysis clinics for their application on the other hand will allow for a worldwide recognised high quality of medical devices, as well as for therapy standards. For instance, the highly efficient treatment mode of hemodiafiltration, promoted by the globally active company Fresenius Medical Care has shown to lead to an improved survival of dialysis patients and a better perceived QoL [46].

With the increasing global number of dialysis patients, manufacturers tended to increase their production capacity of medical disposables in order to profit from the "economy of scale". This allows them to offer medical goods cheaper and thus becoming more competitive. This actual "volume-driven" model, however, is under pressure, when Healthcare Provider Organisations (HPOs) modify their mission statement and focus more on value-based businesses. They undergo a metamorphosis and change from a classical device producer to a therapy provider whilst keeping all necessary activities in one hand. Disease management has become the magic word, which has now opened new ways for HPOs.

Innovative managerial processes dedicated to vertical integration have turned out to be one reason for this new way to success. A close link to international global customers and thorough analyses of markets and needs has further led to a better understanding of different healthcare cultures. Through combining sectors of opportunities for cost reduction, such as in sales, by bundle and care contracts, as well as services with focus on disease management, customer and market needs could be recognized and an optimal use of financial resources obtained (Fig. 10.10). "Medical device innovation— ***is better good enough***?" asks the New England Journal of Medicine in its editorial in 2011 [47] and proposes a model-based approach for the improvement of medical device technology and its evaluation by well documented

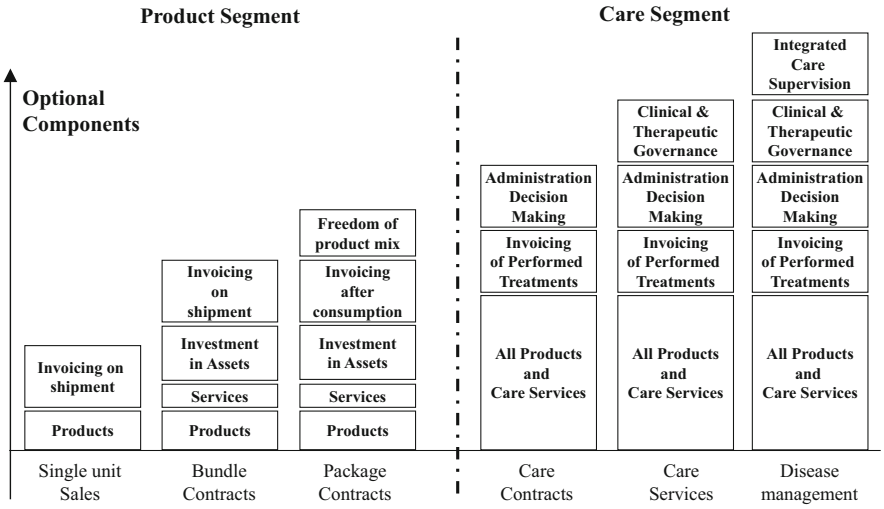

Fig. 10.10 A healthcare system is based on value related to two segments, products and care delivery. The concept of vertically integrated companies in MedTech bases on combining these segments in order to cope with both the needs of customers (patients) in international markets and payers under a single-handed control. The sequential steps until its final stage are shown here with the final result in the right-hand column. This model covers aspects from "device sales", bundle contracts for the delivery of all necessary medical devices, care contracts with hospitals, care services to "disease management". It allows for a better exploitation of financial resources and a higher return-on-investment (ROI) for the respected company

clinical applications. Vertically integrated companies may be the optimal model to cope best with the challenges in the medical device field.

Conclusion

Demographic changes, limited healthcare budgets and performance-based attitudes for medical therapies have led to Pay-for-performance programs in healthcare. Here, consumer (patient), provider (physicians and nursing staff) and payer (patient and health insurance funds) are all involved. To reach targets based on measurable quality indicators, incentives are provided for the efficient use of medical resources and medical devices. The establishment of such key factors needs a consensus among the involved stakeholders to be successful. This consensus can only be reached if the interests of these groups are balanced, beard in mind and special attention is paid to a complex process. Artificial intelligence-based analyses of large patient data bases may be of help in improving this situation. Medical devices underwent a metamorphosis from a simple instrument to a complex tool allowing for sophisticated performances and the active, online interaction with treatment modalities. Innovative devices allow for covering preventively responsibilities in medical care and impact disease management. Vertically structured companies can serve as a model for successful corporates in medical device technology.

Take Home Message

- Demographic changes, limited healthcare budgets and performance-based attitudes for medical therapies have led to Pay-for-performance programs in healthcare.
- Pay-for-performance programs in healthcare are able to increase perceived Quality of Life (QoL) in patients but are not successful in reaching the desired endpoint of a lower mortality.
- Artificial intelligence-based analyses of large patient data may be of help in improving this situation.
- Medical devices underwent a metamorphosis from a simple instrument to a complex tool allowing for the active and online interaction with treatment modalities to achieve patient-specific improvements of care.
- The performance of medical devices has reached a higher level of perfection through a "systems approach" which bears in mind a synergistic action of all involved devices and actors.
- Innovative devices allow for covering preventive responsibilities in medical care.
- Vertically structured companies are the model for successful corporates in healthcare.

References

1. OECD Library (2019) Health at a glance 2019
2. OECD (2010) Health care systems: getting more money for value OECD economics department policy Notes, Nr 2
3. Ayanian JZ, Hamel MB (2016) Transforming primary care, we get what we pay for. N Engl J Med 374:2390–2392
4. Cassel CK, Conway PH, Delbanco SF, Jha AK, Saunders R, Lee HT (2014) Getting more performance from performance measurement. N Engl J Med 371:2145–2147
5. Roland M, Campbell S (2014) Successes and failures of pay for performance in the United Kingdom. N Engl J Med 370:1944–1949
6. Bonfrer I, Figueroa J, Zheng J, Orav EJ, Jha A (2018) Impact on financial incentives on early and late adopters among US hospitals: observational study. BMJ 360:j5622
7. Dummer J (2007) Healthcare performance and accountability. Int J Health Care Quality Ass 20: 34–39
8. Epstein AM, Lee TH, Hammel MB (2004) Paying physicians for high-quality care. N Engl J Med 350:406–410
9. Bardach N, Wang JJ, DeLeon SF, Shih SC, Boscardin WJ, Goldman LE, Dudley LE (2013) Effect of pay-for-performance incentives on quality of care in small practices with electronic health records: a randomized trial. JAMA 310:1051–1059
10. Cutler TW, Palmieri J, Khalsa M, Stebbins M (2007) Evaluation of the relationship between a chronic disease care management program and California pay-for-performance diabetes care cholesterol measures in one medical group. J Manag Care Pharm 13:578–588. https://doi.org/10.18553/jmcp.2007.13.7.578

11. Van Herck P, DeSmedt D, Annemans L, Remmen R, Rosenthal M, Sermeus W (2010) Systematic review: effects, design choices, and context of pay-for-performance in health care. BMC Health Serv Res 10:247
12. Roland M (2012) Pay-for performance: not a magic bullet. Ann Intern Med 157:912–913
13. Eijkenaar F (2011) Key issues in the design of pay for performance programs. Eur J Health Econ 14:117–131
14. Kristensen S, Meacock R, Turner A, Boaden R, McDonald R, Roland M, Sutton M (2014) Long-term effect of hospital pay for performance on mortality in England. N Engl J Med 371: 540–548
15. OECD Library (2020) Health at a glance Europe 2020
16. German Federal Statistical Office. Press release on June 21st, 2021
17. Campbell S, Braspenning J, Hutchinson A, Marshall M (2003) Research methods used in developing and applying quality indicators in primary care. British Med J 326:816–819
18. Doran T, Roland M (2010) Lessons from major initiatives to improve primary care in the United Kingdom. Health Aff 29:1023–1029
19. Doran T, Fullwood C, Gravelle H, Reevers D, Kontopantelis E, Hiroeh U, Roland M (2004) Pay-for-performance programs in family practices in the United Kingdom. N Engl J Med 355: 375–384
20. Roland M (2010) Lessons from major initiatives to improve primary care in the United Kingdom. Health Aff 29:1023–1029
21. Mainz J (2003) Defining and classifying clinical indicators for quality improvement. Int J Quality Healthcare 15:523–530
22. Testa M, Simonson D (1996) Assessment of quality-of-life outcomes. N Engl J Med 334:835–840
23. Thiyagarajan J, de Carvalho I, Peña-Rosas JP, Chadha S, Mariotti S, Dua T et al (2019) Redesigning care for older people to preserve physical and mental capacity: WHO guidelines on community level interventions in integrated care. PLoS Med 16(10):e1002848
24. Altman H, Huang T, Breland Y (2018) Design thinking in healthcare. Prev Chronic Dis 15:e117
25. European Parliament and Council (2017) Regulation (EU) 2017/**7**46 of the European parliament and of the council of 5 April 2017 on *in vitro* diagnostic medical devices and repealing directive 98/79/EC and Commission Decision 2010/227/EU; Official J European Union, L 117/176
26. European Parliament and Council (2017) Regulation (EU) 2017/745 of the European parliament and of the council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC, Official J European Union, L 117/1
27. US Food & Drug Administration (2020) Biological evaluation of medical devices—Part 1: evaluation and testing within a risk management process. Guidance for Industry and Food and Drug Administration Staff. CDRH-Guidance@fda.hhs.gov
28. European Parliament and Council (2007) Regulation (EC) No 1394/2007 of the European parliament and of the council of 13 November 2007 on Advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, Official J European Union, L 324/121
29. Lasker M (1957) The Lasker legacy. www.laskerfoundation.org
30. McNulty P (2009) Keynote on a tale of two sectors. Presentation at US Compliance week Conference 2009
31. Vanholder R, Davenport A, Hannedouche T, Kooman J, Kribben A, Lameire N et al (2012) Reimbursement of dialysis: a comparison of seven countries. J Am Soc Nephrol 23:1291–1298
32. Berwick D (2019) Elusive waste, the Fermi paradox in US healthcare. JAMA 322:1458–1459
33. Shrank W, Rogstad T, Parekh N (2019) Waste in the US health care system. Estimated cost and potential for savings. JAMA 322:1501–1509
34. Statistica (2021) Number of European patents granted in medical technology in 2020. www.statista.com/statistics/1000661/european-patents-granted-in-medtech/. Accessed 28 June 2021

35. BvMed (2021). www.bvmed.de/de/recht/was-sind-medizinprodukte. Accessed 28 June 2021
36. Fresenius Medical Care (2020) Brochure "ESRD patients in 2019, a global perspective"
37. Usvyat L, Raimann J, Carter M, van der Sande F, Kooman J, Kotanko, Levin N (2012) Relation between trends in body temperature and outcome in incident haemodialysis patients. Nephrol Dial Transplant 27:3255–3263
38. Bouchard J, Mehta R (2009) Volume management in continuous renal replacement therapy. Semin Dial 22:146–150
39. Moissl U, Arias-Guillé M, Wabel P, Fontseré N, Carrera M, Campistol JM, Maduell F (2013) Bioimpedance-guided fluid management in haemodialysis patients. Clin J Am Soc Nephrol 8: 575–1582
40. Basso F, Berdin G, Virzì GM, Mason G, Piccinni P, Day S, Cruz D, Wjewodzka M, Giuliani A, Brendolan A, Ronco C (2013) Fluid management in the Intensive Care Unit: bioelectrical impedance vector analysis as a tool to assess hydration status and optimal fluid balance in critically ill patients. Blood Purif 36:192–199
41. Zheng Li-Tao D, Zhen C, Yue Z, Li-Jun G, Wang T (2009) Correlation between pulse wave velocity and fluid distribution in haemodialysis patients. Blood Purif 27:248–252
42. Gross M, Maierhofer A, Tetta C, Sénecal L, Canaud B (2007) Online clearance measurement in high-efficiency hemodiafiltration. Kidney Int 72:1550–1553
43. von Platen P, Pomprapa A, Lachmann B, Leonhardt S (2020) The dawn of physiological closed-loop ventilation—a review. Crit Care 24:121–132
44. Delbeck S, Vahlksing T, Leonhardt S, Steiner G, Heise M (2019) Non-invasive monitoring of blood glucose using optical methods for skin spectroscopy-opportunities and recent advances. Anal Bioanal Chem 411:63–77
45. Patel S, Topping A, Ye X, Zhang H, Canaud B, Carioni P, Marelli C, Guinsburg A, Power A, Duncan N, Kooman J, van der Sande F, Usvyat L, Wand Y, Xu X, Kotanko P, Raimann J (2018) Association between heights of dialysis patients and outcomes: results from a retrospective cohort study of the international MONitoring Dialysis Outcomes (MONDO) database initiative. Blood Purif 45:245–253
46. Maduell F, Moreso F, Pons M, Ramos R, Mora-Macià J, Carreras J, Soler J, Torres F, Campistol J, Martinez-Castelao A (2013) High-efficiency postdilution online hemodiafiltration reduces all-cause mortality in hemodialysis patients. Am Soc Nephrol 24:487–497
47. Suter L, Paltiel D, Rome B, Solomon D, Golovaty I, Gerlovin H, Katz J, Losina E (2011) Medical device innovation—is "better" good enough? N Engl J Med 365:1464–1466

Part V
Problems and Opportunities

Chapter 11
The Role of Medical Devices in Healthcare Sustainability

Carlo Boccato, Sergio Cerutti, and Joerg Vienken

Abstract The sustainability is an important issue for the human activities and the healthcare system cannot escape this rule. The extensive use of medical devices has an impact in worsening the issue (e.g. due to the large number of disposable items), but also helps to solve the problem if the overall picture is kept in mind.

When discussing about healthcare sustainability, the decision-makers should consider, besides the environmental impact, the social and financial consequences. All those aspects are strongly influenced by the aging of the population and the need to extend the adequate treatment to the whole world community.

After a first definition of what is intended as sustainability in healthcare and an analysis of the main relevant issues, this chapter considers the contribution of medical devices and related technologies to this important topic.

Introduction

The sustainability of our way of life is facing many challenges, involving ecological, financial and social aspects. The healthcare (HC) system is similarly confronted with these challenges, substantially due to the increasing complexity of the medical treatments, the aging of the population and the economic inequality.

Inequality among people is a very important issue. The availability of a good level of healthcare for all the individuals and communities, without limitations due to social and economic conditions or to country and continent of residence, is matter of social justice.

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The topic of healthcare sustainability has many correlations with the availability and use of medical devices. They have a strong potential in providing a good and sustainable level of care to individuals and populations, but the impact of their manufacturing and operation on the use of resources and on the environmental pollution should be systematically managed.

In the following pages it will be outlined what it is intended as sustainable healthcare (HC) and what are the challenges that the HC system worldwide is facing now. Then, the contribution of medical devices will be analysed.

11.1 The Healthcare System Sustainability and Its Enemies

The Brundtland Report [1] defines as *sustainable* any activity that "*meets the needs of the present without compromising the ability of future generations to meet their own needs*." [1].

This definition is applicable also to the healthcare systems and embraces several aspects. These aspects should focus not only on the environmental protection and the economic development but also on the very organization of the society. Besides the attention to future generations, the definition of sustainability must include the issue of "social sustainability", intended as the need to ensure the adequate quality of life to people with lower wealth conditions or being located in low resources areas of the world. A discriminatory society cannot be sustainable.

The complexity of our society and the presence of many actors and stakeholders requires to afford all the emerging problems with a systemic view. This is especially true for the HC system sustainability [2, 3]. The key issues undermining the HC system sustainability can be classified into sociopolitical, financial and environmental factors, as summarized in Fig 11.1.

Sociopolitical Issues The inequality of income, and the consequent access to HC services, creates important disparity among people in different geographic areas or belonging to different social classes in the same (even wealthy) country (see Chap. 12). As of year 2017, less than half of the global population is taken care by essential health services [4]. This inequality, besides being morally unacceptable, may undermine the path of the international community to a sustainable development. Ensuring healthy lives and promoting well-being at all ages has been included in the Goal 3 of the UN for a sustainable development [5–7].

Demographic changes, such as the aging of population are other social aspects that strongly influence the sustainability of the system. Besides the cost of the chronic therapies, it also creates a high need for assistance, frequently involving relatives (often not young themselves) as lay caregivers. This gives an additional burden on social organization and economy, e.g. in terms of missed work opportunity.

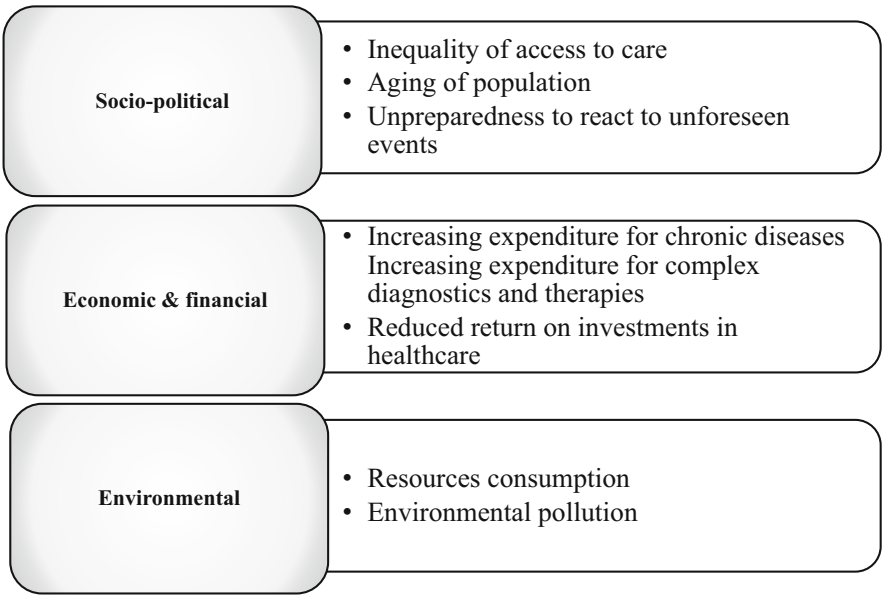

Fig. 11.1 Factors undermining the healthcare system sustainability

An additional issue is the need to rapidly and efficiently react to unforeseen events (or so-called *black swans*)[1] like pandemic or natural calamities. The recent and not yet resolved crisis generated by Corona viruses has shown that the actual pandemic, in addition to the human and economic injuries, has also created disruptions in the HC systems. This, potentially reversing decades of improvement, has also interrupted the campaigns for immunization against other communicable diseases [4]. This made clear the need to revisit the HC policies toward the improvement of system resilience and larger availability of care services.

Economic and Financial Issues As mentioned above, now people live longer, but with an increasing burden of chronic or non-communicable diseases (NCD), usually requiring long-term and often complex and expensive therapies. NCD include Parkinson and Alzheimer disease, diabetes, chronic kidneys disease, strokes, osteoporosis and others.

Living longer, but with the burden of (heavy) disability is one of the main factors undermining he financial sustainability of the HC systems. The decision- and policymakers are struggling with these aspects [9].

[1] Nassim Nicholas Taleb in his book of 2007 [8], introduced the concept of *black swan* referring to the extreme impact of rare and unpredictable events and the human tendency to find a retrospective simplistic explanation for these events.

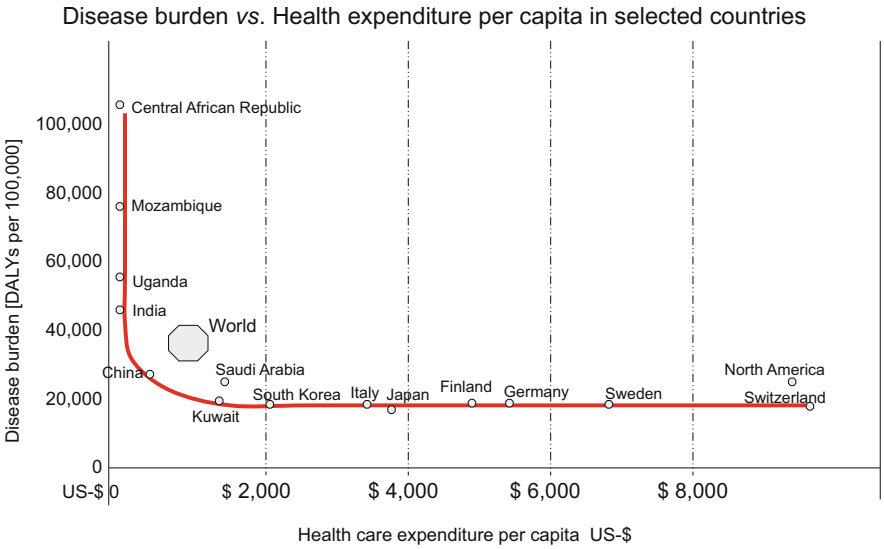

Fig. 11.2 Disease burden vs healthcare expenditure in selected countries. (Adapted from [11])

The DALY[2] parameter can give a synthetic estimation of the overall health quality. The curve in Fig. 11.2 shows the fact that even in front of a healthcare expenditure growth, at least in most wealthy countries, the DALY level does not show a consequent improvement.

The curve in Fig. 11.2 highlights two different topics.

While there still is a considerable space for improvement in many low-income countries, generally characterized by low-resources settings, the most affluent countries are facing a reduction in marginal return on the investment in HC expenditure. This requires a change in HC paradigm favouring a better attention to the delivery of services with real value for the patients (see also Chap. 1).

In addition, this "saturation effect" shows that, having thankfully found therapies for many diseases, we have now to focus on "more difficult" disorders requiring heavier effort in terms of research and more expensive therapies. This is a strong call for policy makers to support research and development of new therapy options (e.g. personalized and precision medicine) aiming at the reduction of diseases burden.

Environmental Issues The production and use of medical devices generate an increasing demand for energy and natural resources (e.g. highly purified water for

[2]Disability Adjusted Life Years—This parameter synthesizes the disease burden on a population due to the years lost for premature mortality and the lower quality of life due to illness or disability (see e.g. [10]). It is computed as: DALY = YLL + YLD. (YLL= years of life lost, YLD = years with disability).

haemodialysis treatment, medical-grade polymers and blends thereof, see also Chap. 2). In addition, the production and disposal of single-use items stress the issue related to the management of possibly contaminated and infectious medical wastes.

The consequences of the environmental impact derived from the extensive application of medical devices of different complexity is becoming more and more relevant due to:

- The extensive use of large number of *resources-demanding* pieces of equipment (e.g. requiring an important amount of energy or water)
- The application of medical-devices-based therapy to a large and increasing part of the population, often affected by chronic diseases requiring long-term and possibly complex treatments
- The extensive use of single-use (disposable) items. This while is decreasing the risks due to cross infection/contamination require high level of resources consumption for their production, and contribute to the creation of potentially contaminated wastes.

Every year an estimated 16 billion injections are administered worldwide, but not all of the needles and syringes are properly disposed of afterwards. Open burning and incineration of healthcare wastes can, under some circumstances, result in the emission of toxic compounds, such as chlorine, dioxins, furans, and most recently particulate matter (e.g. PM 2.5 and PM10).

As a first conclusion, the factors affecting the HC sustainability span from the use of financial resources to the environmental pollutions to some more "socio-political" issues like access to care and decision on investments versus clinical outcome evaluation (see also Chap. 9). All these aspects influence the citizens' expectations and are matter of political as well as technical choices [12].

11.2 Health Care Systems Sustainability and the Impact of Medical Devices

The possible contribution that the application of medical devices can give to sustainability is summarized in Fig. 11.3.

A current model [13] underlines the elements to keep a healthcare system sustainable. Among others, it is useful to consider this index and its vital signs to be evaluated:

- **Access**: Extent to which medicines, treatments, diagnostics or other technology can be accessed by those who need them
- **Health status**: Actual health status and outcomes
- **Innovation**: Developing new and transformative medicines, treatments and technology

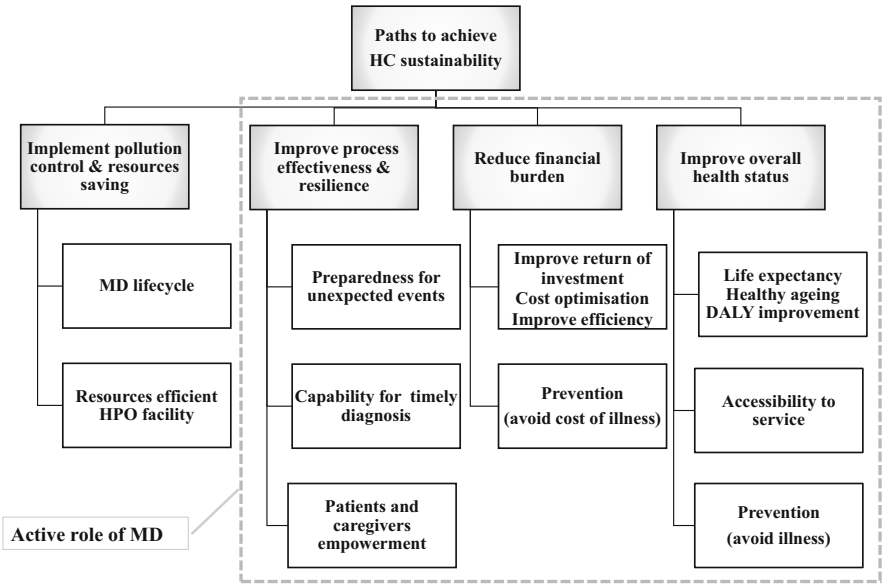

Fig. 11.3 The contribution of medical devices to the healthcare system sustainability. (*HC* Healthcare, *MD* medical device, *HPO* Healthcare Provider Organisation, *DALY* Disability Adjusted Life Years). (Basic concept derived from [13])

- **Quality**: Frontline delivery of healthcare
- **Resilience**: Ability of a healthcare system to continue to meet the populations' needs in the future

According to Fig. 11.3, it is possible to identify the main influences of the medical devices to the sustainability of the HC systems.

A first level of contribution is achieved with the environmental-aware design and operation of medical devices during their full lifecycle. This means to consider the environmental impacts of a medical device from its conceptual definition, to the production, to the use and finally to the disposal or decommissioning. The ultimate goal is, without sacrificing the safety and performance, to achieve the most effective use of resources and the lowest production of waste.

A more *active* contribution of the medical devices is in the achievement of a more effective and efficient medical treatments as well as the support that the related technology can give to the extension of care to a larger part of the population, e.g. through self-monitoring devices or telemedicine techniques (see dashed area in Fig. 11.3).

11.2.1 Pollution Control and Resources Saving

In recent years, increasing attention has been paid to the reduction of the resources consumption and waste production in the medical sector, spanning from the careful design of the production process, including the disposal of toxic solvents, to the correct disposal of the expended items. In addition, a careful design of environmentally friendly healthcare buildings is more and more realized.

For instance, the haemodialysis treatment for kidney patients can be considered as a paradigm for the above aspects. The haemodialysis is a long-term chronic treatment (see details in Chap. 6) involving:

- The use of a complex medical equipment (e.g. the dialysis monitor)
- Dialysis fluids and concentrates requiring about 400 L of purified water per treatment. Special (single use) disposable items (like blood lines, dialysis filters, needles, etc.)
- Waste of the spent dialysis fluid during the treatment and disinfecting agents for the cleaning/disinfection of the dialysis monitor
- Energy requirement for the dialysis monitor up to 3.5 kWh per treatment [14].

In addition, a total of 694 kg of waste per patient per year is produced. Most of this waste is potentially infective [13].

Furthermore, due to the high number of disposable items used in haemodialysis, the consumption of energy and the CO_2 production for the delivery of the needed material at the dialysis center should not be neglected.

Many international organizations and private companies dealing with dialysis treatment have initiated, since many years, several initiatives to reduce and control the environmental impact of the haemodialysis related devices.

Among the most relevant recommendations it is possible to list the following:

- Rationalize the use and reuse of the RO discarded water and of the spent dialysis fluid [14–17]
- Optimize electric energy consumption
- Rationalize the waste management
- Reduce the negative externalities, e.g. producing the dialysis concentrate inhouse from highly concentrated media and avoid the transportation of bulky container of dialysis concentrate composed by high percentage of water.

The achievement of a better level of sustainability needs also to consider the overall MD lifecycle.

Attention to sustainability issues should start right from the device's conception and design.

As an example, the IEC 60601-1-9[3] is a collateral standard to the IEC 60601-1 concerning the safety and basic performance of medical electrical equipment.

It aims at improving the environmental impact of an electrical MD through all stages of the device's lifecycle, from the very conception to the end of life. To claim compliance with this standard the manufacturer should consider and document the actions taken to minimize the environmental impact over the full lifecycle of the device.

It is related to other standards, like

- ISO 14971(Medical devices—Application of risk management to medical devices) [18], since the environmental impact must be considered among the element of the risk management process. Among others, it considers the risks connected with possible chemical or biological hazard and emission of toxic substances.
- ISO 14001 (Environmental management systems—Requirements with guidance for use) [19] addresses the implementation of processes for the management of the environmental impacts over the full product's lifecycle.

In addition, the manufacturer should also demonstrate that the expected medical benefits justify the possibly unfavourable environmental impacts generated by the equipment. This evaluation may be influenced by the intended use of a device. The impact accepted for a life-saving equipment may not be tolerated for a device intended for easier conditions or for aesthetic applications.

An additional action to reduce the environmental impact of the medical equipment is relevant to the HPO design. The accommodation and effective operation of complex medical equipment requires also the correct adaptation of the HPO facility where the equipment is installed and operated.

It is important that the facility allows the safe disposal of the exhausted and possibly contaminated parts and fluids, e.g. used personal protective equipment, dialysis filters, drain fluids (see also Chap. 6).

11.2.2 Active Contribution of Medical Devices to Sustainability

Making reference to Fig. 11.3, it is possible to see that the medical devices can have an important "active role" in the achievement of the HC system sustainability

This *active* contribution is highlighted in dashed area of Fig. 11.3.

The costs issue is surely the most evident and discussed aspect when talking about healthcare sustainability.

[3] Medical electrical equipment—Part 1–9: General requirements for basic safety and essential performance—Collateral Standard: Requirements for environmentally conscious design.

As shown in Fig. 11.2, the costs for healthcare are continuously rising even if the overall disease burden (DALY) is not linearly improving with the invested resources.

The way to cope with these issues is to implement a paradigm change [3], based on:

- **Patient's empowerment**. Especially when dealing with a chronic treatment, it can reduce the involvement of professional caregivers and the need for the patient to go to hospital for ambulatorial checks. In this case the availability of medical devices engineered for simple, safe and reliable operation by lay users is a key point.
- **Data collection and sharing**. The sharing among medical staff, possibly located in distant locations, allows for a cooperative diagnosis or for an agreement on the therapy in case of difficult clinical situations. This supports a higher quality of medical care also in remote locations or to small hospital with less resources.

The possibility of remote medical consultation is of special importance in case of natural catastrophes but can also help in building a monitoring and safety network to control a pandemic spread.

The patient's empowerment is considered [20] among the main pillars to ensure the sustainability of the healthcare system. The empowerment of the patients and of the lay caregivers may in fact reduce the cost, but can also improve the quality of the care and the quality of life (QoL) of the patient. The availability of devices that enables the patients to measure the required parameters him/herself can save resources, due to the less need for qualified personnel to take care of "easy" tasks.

This also allows the monitoring of the important parameters at the right time, that may not always be possible with the traditional ambulatory consultation (see case story in Chap. 5).

A basic requirement is that these parameters are reliably collected, stored and made available to the professional caregiver in due time.

Sustainability means also "healthy ageing". Due to the increasing percentage of elder population and the consequent prevalence of chronic diseases, the HC system, to be sustainable, needs to address the way to promote the healthy and autonomous ageing. This means to ensure a better and self-sufficient life in the last part of the existence, but also preventive actions and considerable saving in avoiding acute costly treatments when avoidable [21]. The remote consultation supported by easy operable MDs is a way to grant elder patients with the personalized monitoring and grant the most degree of autonomy.

Conclusion

The pervasive application of medical devices in the modern healthcare has many implications on the sustainability of the HC system.

The most evident one is the need for a sensible design and operation of these devices to ensure that resources, like electric energy and water, are effectively used. Considering the large number of disposable items, it is also important that these are adequately disposed. The reuse of these items can in principle be also considered,

but in this case, the reuse process must ensure the safety and efficacy of the reconditioned items. It should also be considered that the reconditioning process is also consuming resources and produce pollution (e.g. spent disinfecting agents). For this reason, a trade-off between disposal and reconditioning should be carefully considered (see also Chap. 6).

Attention should also be paid to the design of the physical environment where the MD is used: the careful design of these areas and locations can contribute to reduce the environmental impact.

The medical devices give an important contribution to the reinforcement of a new paradigm based on the patient's empowerment. The medical equipment can e.g. provide the information about the required physiological parameters in short time directly to the caregivers. In addition to the important cost savings, this last aspect can also contribute to grant a high level of medical therapy to a larger population without restrictions related to geographical location or wealth status.

The patient's empowerment and the easy communication of vital parameters as well as the possibility to obtain quick instrumental data (e.g. from an MRI equipment) evaluated by well-trained experts, possibly remotely located, are important supports for answering to unexpected and critical events as well.

Take Home Message

- The sustainability of the healthcare system is confronted by many challenges, involving environmental, financial and socio-political aspects.
- Medical devices can give a considerable support in improving the HC sustainability, both in terms of better use of resources and supporting a more effective healthcare model.
- The careful use of natural resources and the pollution reduction requires to pay attention to the overall device's lifecycle, from the conception and design to the operation and final disposal.
- Patient's empowerment, prevention of illness, capability for early diagnosis as well as better preparedness to unexpected events are among the most important active contributions that MD can provide to the HC system sustainability.

References

1. United Nations General Assembly (1987) Report of the World Commission on Environment and Development: our common future. Oxford University Press
2. Tainter JA (1988) The collapse of complex societies. Cambridge University Press
3. Barile S, Orecchini F, Saviano M, Farioli F (2018) People, technology, and governance for sustainability: the contribution of systems and cyber-systemic thinking. Sustain Sci 13:1197–1208
4. UN development goal 3. Good health and well-being: why it matters. https://sdgs.un.org/goals/goal3. Accessed 9 June 2021

5. UN development goal 3. Ensure healthy lives and promote well-being for all at all ages. https://www.un.org/sustainabledevelopment/health/. Accessed 9 June 2021
6. UN development goal 3. Good health and well-being: why it matters Why-It-Matters-2020.pdf (un.org). Accessed 9 June 2021
7. Reinhart E, Daves D, Maybank A (2021) Structural medicine: towards an economy of care. Lancet. https://doi.org/10.1016/S0140-6736(21)00937
8. Taleb NN (2007) The Black Swan: the impact of the highly improbable. Random House
9. Danovi A, Olgiati S, D'Amico A (2021) Living longer with disability: economic implications for healthcare sustainability. Sustainability 13:4467. https://doi.org/10.3390/su13084467
10. Friedman HS (2020) Ultimate price: the value we place on life. University of California Press, Oakland, CA
11. M R and H R (2016) Burden of disease. Published online at OurWorldInData.org
12. Lehoux P (2006) The problem of health technology. Taylor & Francis Group, New York
13. https://futureproofinghealthcare.com. Accessed 9 June 2021
14. Kastl J, Pancirová J (eds) (2011) Environmental guidelines for dialysis—a practical guide to reduce the environmental burden of dialysis. EDTNA-ERCA and Fresenius Medical Care
15. Tarrass F, Benjelloun M, Benjelloun O (2020) Power from the sewer: renewable generation of electricity from hemodialysis effluent water. Nephrol Dial Transplant 1–2. https://doi.org/10.1093/ndt/gfz286
16. Tarrass F, Benjelloun M, Benjelloun O, Bensaha T (2010) Water conservation: an emerging but vital issue in haemodialysis therapy. Blood Purif 30:181–185
17. Boccato C, Evans D, Lucena R, Vienken J (2015) Water and dialysis fluids a quality management guide. Pabst Science Publishers, Lengerich
18. ISO 14971:2019 Medical devices—application of risk management to medical devices
19. ISO 14001:2015 Environmental management systems—requirements with guidance for use
20. Russo G, Moretta Tartaglione A, Cavacece Y (2019) Empowering patients to co-create a sustainable healthcare value. Sustainability 2019(11):1315. https://doi.org/10.3390/su11051315
21. WHO healthy ageing and the sustainable development goals. https://www.who.int/ageing/sdgs/en/. Accessed Mar 2021

Chapter 12
Medical Devices in Low- and Middle-Income Countries

Steffen Fleßa

Abstract The demand for medical devices is constantly growing all over the world. However, most managers of healthcare technology and medical devices tend to neglect the growing markets of middle- and low-income countries. A thorough analysis of the growing and aging population in these countries, the income distribution and the improving social protection demonstrates that there is a demand for simple and cheap as well as for sophisticated devices with a huge market in these countries. Enterprises producing medical devices should focus on the needs and preferences of people in low- and lower-middle-income countries. They need to get acquainted to the specifics of cultures and markets and start cooperation and joint ventures soon—otherwise they will lose these markets.

Introduction

Most politicians, scientists and chief executive officers would agree that innovative medical devices are invented, produced and sold primarily in the richer countries of this world. The poor—this is the assumption—cannot afford expensive equipment, implants, etc. and, thus, do not constitute a market for "our" products. The reality, however, is different. About half of humans lives in low- and middle-income countries. Even if only 5% of them have the means to buy modern healthcare services, this is a tremendous market of 185 million potential customers [1].[1] At the same time, there is a strong effort to implement (social) health insurances in most of these countries frequently covering medical services based on sophisticated medical devices. And the majority of these countries demonstrate economic growth rates that are admirable. Within a few years Southern America, Asia and even Sub-Saharan Africa might be the most important markets for medical devices.

[1] Statistics of this chapter are—if not mentioned differently—based on the most recent World Development Indicators published by the World Bank.

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In this chapter we will analyze the potential of markets for medical devices in low- and middle-income countries. In the first subsection, we will examine the world health situation. In the second subsection, we will focus on healthcare for the poor of today and discuss what kind of equipment is needed for them. The last subsection will concentrate on the emerging economies of today and in future as well as their potential for becoming key-customers of medical devices.

12.1 Many Worlds of Health

The first simple—but fundamental—statement is that we live in many worlds of health [2]. This statement is true for differences in healthcare and health between countries, but also between regions and social groups of different countries. In the so-called developed world, the majority of people benefit from social insurances based on some kind of solidarity, but universal health coverage is still unaffordable for many countries. Thus, the rich of these countries live in another world of health than the poor. At the same time, we do not have a universal solidarity system so that different countries experience completely different healthcare situations. These discrepancies have a tremendous effect on the demand for medical devices and call for a thorough analysis of healthcare systems and health in different regions. In this section, we will distinguish countries by their economic potential and demonstrate the consequences on the health status of their population.

12.1.1 Classification

There is a *Babylonian confusion* resulting in a wrong perception of the reality of the majority of the world population [3]. We talk about "developing countries", "underdevelopment", "third world", "low, middle, high income countries", "indebted countries", "developed world", "industrialized world", etc. The terms "developing countries", "underdevelopment", "developed world" and "third world" are obsolete and will not be used in this chapter. However, the other terms still have some relevance and can be distinguished [4]:

- **Growth and development**: Economic growth refers to the increase of national product resulting in wealth and income of people. Development implies an increase of complexity of a society based on division of labour, increased trade, communication and productivity. Development is a long-term prerequisite of economic growths, but growth can also be achieved in the short-run by exploiting national resources and neglecting social investments.
- **Dynamic and static development**: Most development concepts focus on certain statistic, such as national product per capita, mortality rate or diversification of production. If a value of a statistic (or an index number) is above or below a

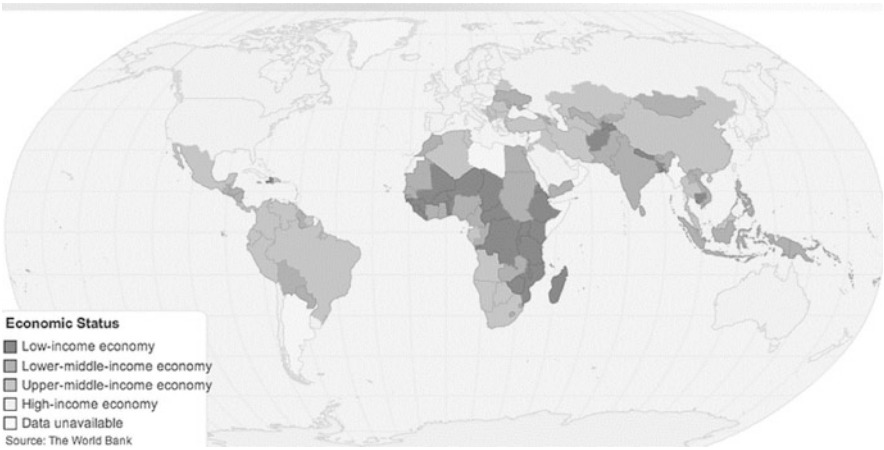

Fig. 12.1 Country income groups [7]

certain level, a country is called "developing country". Dynamic concepts analyze the change of the potentials of a society, e.g. increase of productivity or human workforce. It may happen those so-called developing countries do not develop at all— in a dynamic sense—while so-called developed countries strongly develop.

In this chapter, we will distinguish countries based on the official World Bank classification of low, lower-middle, upper-middle and high-income countries, a discrimination purely based on the gross national income per capita.[2] The four categories for the fiscal year 2019 are [5]:

- **Low-income countries**: 995 US$ or less, e.g. Afghanistan, Gambia, Haiti, Nepal.
- **Lower-middle-income countries**: 996–3895 US$, e.g. Angola, Bangladesh, Tunisia.
- **Upper-middle-income countries**: 3896–12,055 US$, e.g. Mexico, Iran, Algeria.
- **High-income countries**: 12,056 US$ and above, e.g. USA, Germany, Cayman Islands.

Figure 12.1 shows a world map with the World Bank classification of the year 2016. The methodology adjusts for inflation so that changes between the groups demonstrate real effects of economic development. However, for all categories the real economic strength has been continuously increasing during the last decades. Figure 12.2 shows that even the poorest countries have increased their income per capita, and many countries which are upper-middle-income countries today have been low-income countries before (e.g. Malaysia, Thailand), while several countries have made their way from low to lower-middle-income countries, such as Zambia, Vietnam, Kenya, Laos and Cambodia [6].

[2] World Bank Atlas Method.

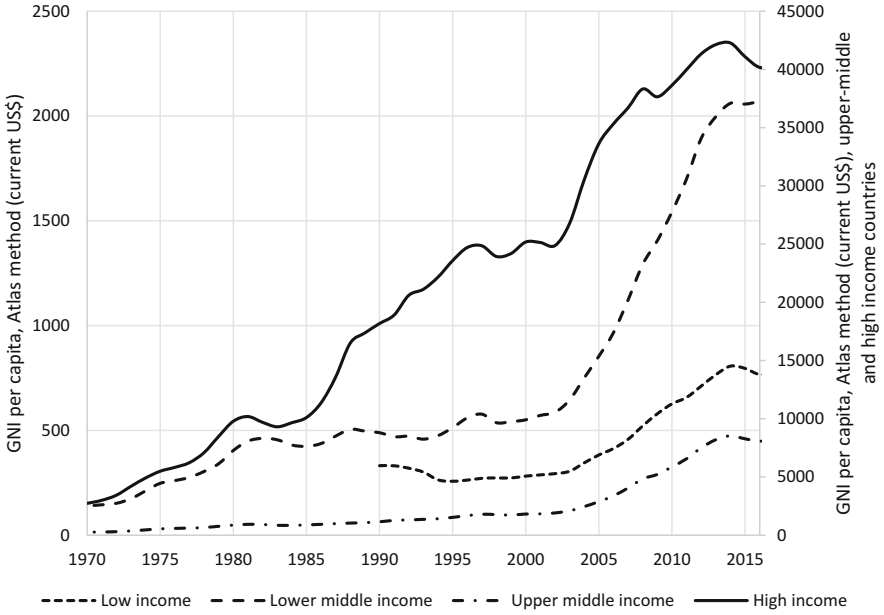

Fig. 12.2 Economic development worldwide (*GNI* Gross National Income). (Source: own, based on data of [1])

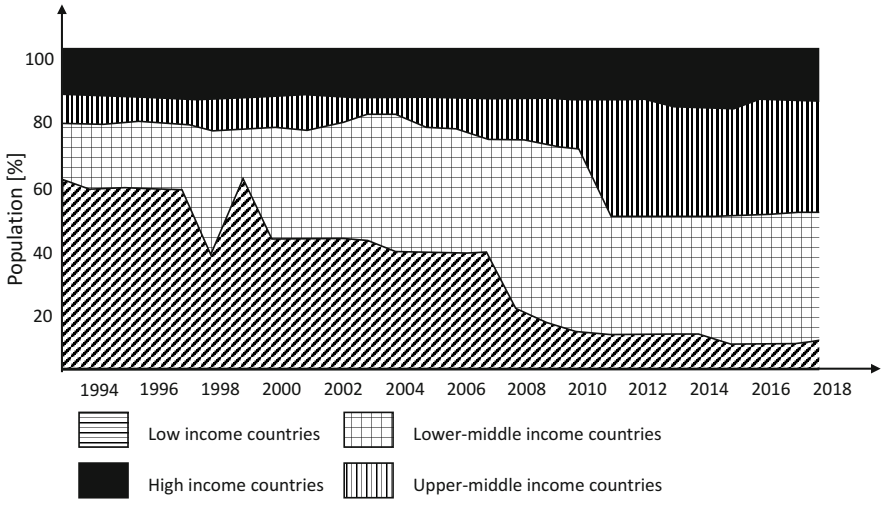

Fig. 12.3 World population by income (1993–2018). (Source: own, based on data of [6])

Figure 12.3 exhibits the world population by country classification [6]. It becomes obvious that the percentage living in high-income countries is rather small (some 18%) and remains rather unchanged. Some 50% of the world

populations lives in low- or lower-middle-income countries—countries which were called "developing countries" in former times. However, this share was up to 80% some 15 years ago. While the population of these poor nations is still growing at a rate that is double as high as in the upper-middle- and high-income countries, many of these poorer countries have made their way into the upper-middle-income group. In 2018, only some 9.7% of the world population lived in very poor countries, in the early 1990, this statistic was still some 60%.

However, poverty is a fact for entire countries and for certain subpopulations. This is a human tragedy and also a challenge to all efforts to export medical devices to these countries, regions and populations. Therefore, it is worthwhile to discuss the health situation in these countries.

12.1.2 Characteristics of Health and Healthcare in Low- and Middle-Income Countries

It is obvious that the national income will result in the availability of financial and non-financial healthcare resources. As Table 12.1 shows, the healthcare expenditure of poor countries is only a fraction of the respective health expenditure of rich countries. The figure is adjusted for purchasing power parity so that different values can be compared. The lowest expenditure per capita per year is shown for the Central African Republic (29.91 Int$), while the highest expenditure is in the USA (9869.74 Int$), i.e. 330 times higher. The poorest countries spend a higher percentage of their national income on healthcare than the lower-middle-income countries, but a higher percentage comes as donations from abroad. Generally, the higher the income class, the higher is also the share of the domestic production dedicated to healthcare.

Financial resources strongly correlate with personnel resources.[3] While Monaco has 52.63 inhabitants per nurse or midwife, the Chad has 3236.25 (factor 61.49). On average, 1217 people have to share one nurse/midwife in low-income countries, 567.96 in lower-middle-income countries, 298.89 in upper-middle-income countries and 115.16 in higher-income countries. For physicians, the figures are even more extreme: in Chad 22,727.27 inhabitants have to share one physician, while in Cuba 135.76 inhabitants are counted per physician (factor 167.41). Again, the number of inhabitants per physician is highly correlated with the income class with 3214.40, 1423.08, 521.73 and 332.45 inhabitants per physician. Unfortunately, no international statistics for medical devices is available, but it is obvious that buildings, equipment and vehicles of healthcare facilities are highly correlated with the healthcare expenditure in these countries.

Table 12.2 shows some health outcomes for country classes. It is obvious that low-income classes are still in the early stages of the epidemiological transition and

[3] The availiability of these statistics in international data bases is limited, i.e. figures must be taken with caution.

Table 12.1 Healthcare resources (most recently available figures) (p.c. per capita) [1]

Class	Nurses and midwives (per 1000 people)	Physicians (per 1000 people)	Hospital beds (per 1000 people)	Current health expenditure (% of GDP)	Current health expenditure p.c. (current Int $)
Low income	0.8219	0.3111	–	5.60%	97.09
Lower-middle income	1.7607	0.7027	0.9860	3.94%	265.80
Upper-middle income	3.3457	1.9167	3.6035	5.81%	959.44
High income	8.6837	3.0080	4.0705	12.53%	5453.29

Table 12.2 Healthcare resources (2016) [1]

	Cause of death				Mortality rate p. 1000		
Class	Group I[a]	Group II[b]	Injuries	Life expectancy	Infant	Neonatal	<5
Low income	50.14%	37.85%	12.0%	62.94	50	27	71.6
Lower-middle income	29.81%	60.78%	9.41%	67.88	38.1	24.6	50.4
Upper-middle income	7.36%	84.38%	8.31%	75.30	12.2	7.4	14.4
High income	6.98%	87.45%	5.59%	80.49	4.7	3.1	5.6

[a]Communicable diseases, maternal, prenatal and nutrition conditions
[b]Non-communicable diseases

group I diseases and conditions (i.e. infectious diseases, maternal, prenatal and nutrition conditions) dominate. However, even in these countries the disease panorama is complex with a rather high prevalence of chronic-degenerative diseases and in particular accidents. Furthermore, the majority of the world population mainly suffers from chronic-degenerative diseases irrespective of their place of living. The table also demonstrates that mortality rates for new-born, infants and under-five strongly depend on the income class. For instance, under-five mortality rate is 12.78 times higher in low-income countries in comparison to high-income countries. Consequently, life expectancy strongly differs on average by almost 17.5 years.

In many aspects, Sub-Saharan Africa is still the region with the worst health outcomes. As Fig. 12.4 shows, the burden of disease (measured as annual loss of disability adjusted life years per 1000 inhabitants is highest in Africa followed by the Eastern Mediterranean and South-East Asian region. Sub-Saharan Africa has the lowest healthcare resources, the lowest ratio of professionals per inhabitant and the poorest health outcomes. The absolute risk of suffering from a chronic-degenerative disease in this region is higher than for high income countries although these

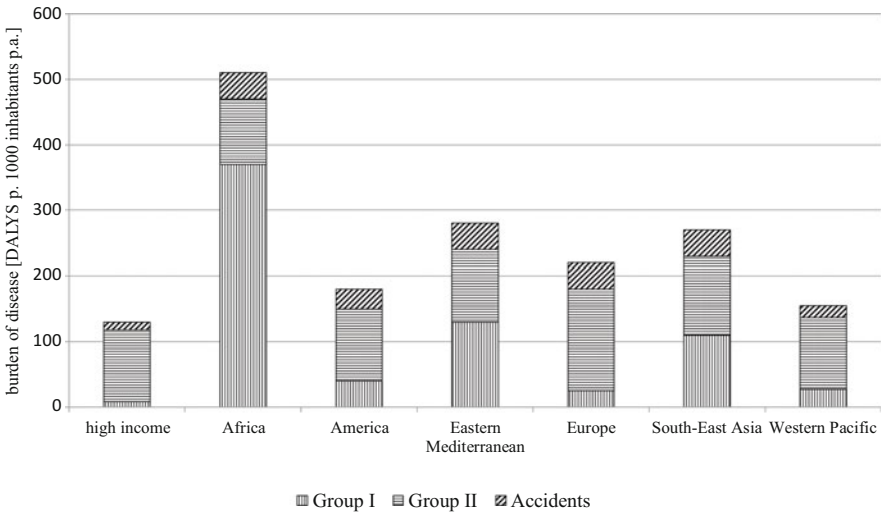

Fig. 12.4 Burden of disease. (Source: own, based on data of [8])

countries are dominated by infectious diseases, i.e. there is a double burden of disease.

Generally, there is a positive correlation between national income and health outcomes, i.e. an increase of 1000 US$ p.c. improves the life expectancy by 0.3 years (comp. Fig. 12.5). For low and middle-income countries, the same increase of income leads to an increase of 3.4 years while for upper-middle- and high-income countries the value is 0.2 years. It is generally accepted that economic growth produces the resources for better health, while better health provides the potential for economic growth and in particular overcoming the poverty-traps [9].

Another characteristic of a low-income country is the unequal distribution of wealth and income which can be demonstrated with a Lorenz chart. As shown in Fig. 12.7, a Lorenz curve is a graphical representation of the distribution of a variable in a population. The curve shows the proportion of this variable. If every person has the same share, the Lorenz curve is the bisector. If the variable is unequally distributed, the Lorenz curve is below the bisector. The double of the area between the bisector and the Lorenz curve is called "Gini Coefficient" as a measure of unequal distribution of that variable.

Low- and lower-middle-income countries usually have higher inequity scores (comp. Fig. 12.6), i.e. the majority of people has very limited resources while few can enjoy tremendous wealth. In many of the poorest countries, the richest 10% have more than 25% of the income, and the number of millionaires in low und lower-middle-income countries is steadily increasing [10]. Figure 12.7 demonstrates this for Cambodia. While 60% of the population have only 30% of the income, the last 10% have 25%. The first 60% are almost equally poor, while the last decile enjoys luxuries on an international level, even in healthcare. The consequence of limited and unequally distributed resources is "many worlds of health" not only on an

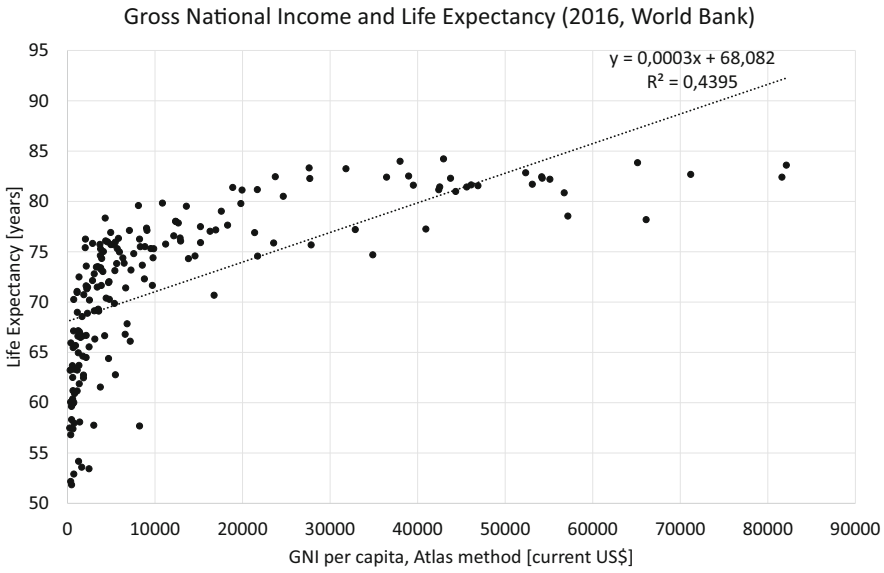

Fig. 12.5 Gross national income and life expectancy (2016). (Source: own, based on data of [1])

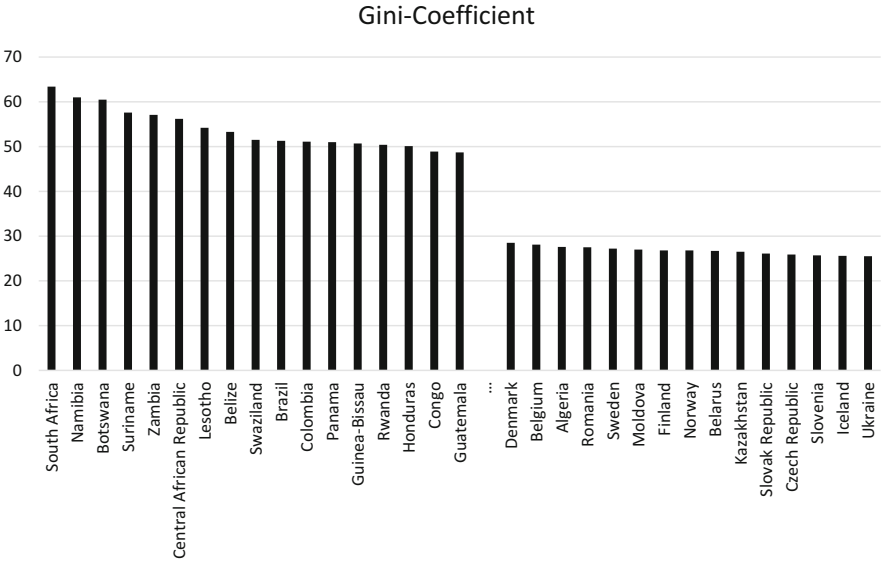

Fig. 12.6 Gini coefficient (different years). (Source: own, based on data of [11])

international scale, but also within one country. The poor and vulnerable in low and lower-middle-income countries are not universally covered even by basic healthcare services, while the rich in these countries have access to international services and

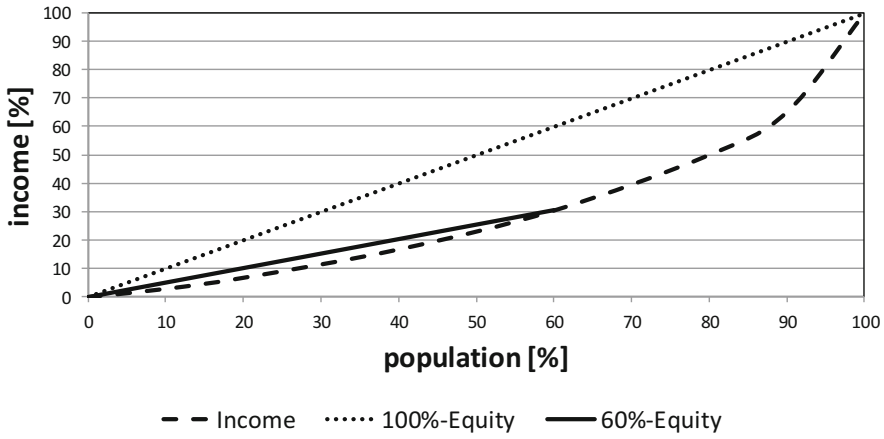

Fig. 12.7 Lorenz chart for Cambodia. (Source: own, based on data of [12])

enjoy state-of-the-art care in their own countries. Consequently, an analysis of the market chances of medical devices has to distinguish between these two groups.

12.2 Applied Technology

The term "Applied Technology" is used for techniques and methods which are not based on international standards but adjusted for a specific situation [9]. Usually, Applied Technologies are simpler, cheaper and smaller than standard technologies and respect perceptions and preferences of the local population. For instance, infusion solutions are usually produced industrially by distillation with high energy consumption and transport costs. Applied Technology produces infusion solutions by reverse osmosis (to produce purified water) locally in hospital laboratories. Other examples are solar sterilization, ramps instead of elevators, basic radiographic systems or locally produced external fixators.

Most Europeans assume that their technology is superior and call for its application in low- and middle-income countries. However, this can induce two problems. Firstly, these technologies are not affordable for the poor and vulnerable of these countries. Secondly, sophisticated technology might not be appropriate for the technical capacity of the local setting. For instance, if no maintenance can be guaranteed, no MRI should be installed irrespective whether it is paid for by donations or not. Local personnel must be able to operate and maintain medical devices or they should not be employed. In addition, sophisticated equipment might do more harm than good. For instance, many rural hospitals in these countries lack trained radiographic personnel. Consequently, one-switch radiographic systems must be used in order to avoid harm of patients caused by wrong radiation doses.

Consequently, we have the following situation for decision-making:

1. If financing of the entire product life cycle can be guaranteed (i.e. not only acquisition, but also costs of maintenance, spare parts, disposal etc.), adequate training of operating personnel and technical maintenance (local engineers and craftsmen), the acquisition of sophisticated technology seems appropriate. In the reality of low- and lower-middle-income countries, purchasing, transport and installation of high-end equipment is financed by international donations while it is expected that the costs of maintenance and spare parts are shouldered locally. The consequence is frequently poor maintenance and early loss of functionality.
2. Applied technology should be employed if the technology is affordable with local resources, maintenance can by guaranteed with local personnel and operating the device is simple.
3. In all other cases, the technology must not be used. The consequence can be that certain diagnostics and therapies are not available.

Dialysis services in Tanzania are an example for a service where applied technology is not available and sophisticated technology should not be employed [13]. The number of studies focussing on the economic feasibility of haemodialysis in low and lower-middle-income countries is limited [14, 15]. We analyzed the cost of haemodialysis at Muhimbili National Hospital in Dar es Salaam for the year 2014. The unit had 10 dialysis beds operating three shifts per day and 6 days a week. The actual cost per haemodialysis was 176 US$—a tremendously high amount in comparison to the local resources. The reasons are amazing. Firstly, materials have to be imported and are more expensive than, for instance, in Germany. Even duties have to be paid for importing these consumables. Secondly, professional staff is extremely scarce in Tanzania resulting in high personnel costs. Nurses and doctors in this department had costs which where up to five times the respective figures from "normal" Tanzanian hospitals. Thirdly, the utilization rate of the unit was rather low so that the cost per haemodialysis was high.

What is the consequence of such a situation? Firstly, we can state that dialysis services amounted to 18,304 US$ p.a. per patient while the health expenditure of this country was only 35.50 US$ p.a. p.c. It is possible to reduce the cost by increasing utilization rate, waiving of tariffs and improved management. But the costs remain tremendously high for a nation like Tanzania. Thousands of Tanzanians die every year due to poor or unavailable healthcare services with diseases which can be cured easily and without major investments. Here we are facing the awful question of healthcare in low resource country which Victor Fuchs asked already in his famous book of 1998 "Who shall live?" [16]. There is no way to make haemodialysis available for all patients with chronic kidney failure of Tanzania. If patients with this disease require haemodialysis and cannot access the service, they will die. And as it looks for today, there is no simple and cheap alternative.

The message for the global medical device industry is clear: there is a great demand for applied technology for billions of people in low and lower-middle-income countries. India has become a market leader in this field. The profit per device is small, but the market is huge. The industrialized world has the technology

to produce simple and cheap alternatives to the sophisticated products. This market is grossly neglected until now.

However, even in a least developed country like Tanzania there is a market for high-end medical devices. As stated before, a small percentage of the population is rich even when considering European standards. The World Wealth Report estimates that some 167,970 High-net-worth individual (HNWI, i.e. individuals holding financial assets with a value greater than US$ one million) lived in Africa in 2017 holding a wealth of 1.7 trillion US$. The number of HNWI in Africa increased by 6.9% in this year [17]. For the Asia-Pacific region the respective numbers were 6.2 million HNWI with a wealth of 21.6 trillion US$ and a growth rate of 12.1%.

A "market of millionaires" needs high-end medical devices in Africa and Asia. They are able and willing to pay for reliable medical services including diagnostic equipment and implants. But even the middle-class of these nations increasingly has resources to pay for better healthcare services. For instance, the Social Health Insurance system of Vietnam covers rather cheap hip prostheses from Asian producers, while European products have to be paid out-of-pocket. As we were informed by the biggest orthopaedic centre in Vietnam, the number of patients requesting these European products is steadily increasing. If we assume that only 10% of Asians and 5% Africans have the means to pay for medical devices from Europe, this is a market of 505 million of US$.

12.3 Emerging Markets: Markets of the Future

In addition, the world markets are constantly changing. Three important developments have to be incorporated in an analysis.

12.3.1 Economic Growth: The New Tigers

Many low and middle-income countries show an economic growth that makes them candidates to become middle-income countries within one generation. As the population of these countries is huge, these countries are the markets of the future for many products, definitely not only for low-end goods. The term "emerging" markets is defined differently by analysts and authors, but all concepts conclude that these economies will become developed markets and active participants in the world economy within the next 20 years [18].

Figure 12.8 shows that the majority of emerging markets are in Asia. China, India, Indonesia, Thailand, and Malaysia alone have a population of 3.021 billion and their economies grow at rates between 5.07 (Indonesia) and 7.17% (India, 2017). Consequently, their demand for healthcare services will also grow inducing an over-exponential growth of demand for medical devices. At the same time, these countries have become producers of medical devices and competitors to their European and

Fig. 12.8 Emerging markets 2013 [19]

American counterparts. Until recently, products from China and India were of low quality and cheap, but more and more they offer high-quality products. At the same time, both countries have well-established personal relationships to South-East Asian countries so that European products face fierce competition. Consequently, excellent quality, customer-orientation, reliable services and needs-oriented marketing of European medical devices become more and more important. Some years ago, European products were too expensive for the majority of customers from these countries, but the rich had no alternatives if they wanted to have reliable products. In future, more people in these counties will afford these products, but they will also carefully choose the provider.

12.3.2 Social Insurance

Until recently, the majority of people living in low and lower-middle-income countries had no health insurance coverage, i.e. health expenditures were paid out-of-pocket. The World Health Organization calls for "universal access" to healthcare services for everybody in this world [20, 21]. "Universal healthcare" (UHC) has the following dimensions: population (who is protected in case of illness?), services (which service is covered in case of disease?) and cost recovery (which part of the total costs in case of disease is covered?). UHC is a central objective of international politics and a sustainable development goal [22]. It is generally accepted that universal health coverage requires that national governments take responsibility for the social protection of their population. Social insurances and subsidy for the poor are the two most important instruments for this [23] (Fig. 12.9).

The World Bank calculates a UHC-coverage index incorporating all three dimensions [1]. The world index of the year 2015 (latest data) was 63.7. Low-income

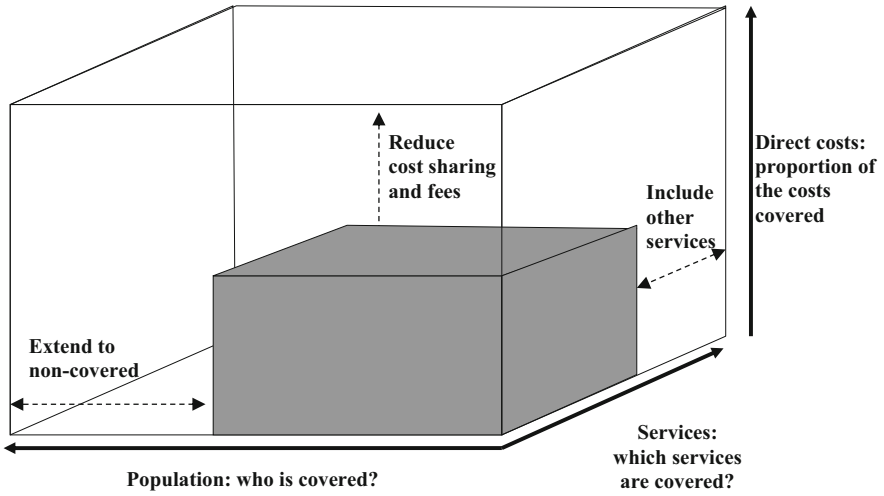

Fig. 12.9 Universal Health Coverage (UHC). (Source: own, based on [23])

countries have a poor index (41.0), high-income countries a high index (80.1) and middle-income countries are found between both extremes. Except for Afghanistan, Pakistan and Yemen, all countries with an index of less than 40 are in Sub-Saharan Africa with Chad as the country with the worst coverage. This data shows that in particular Asian countries have strongly improved the social protection for their population. More and more countries offer social insurance coverage at least for parts of the population [24]. For instance, Cambodia has started a national Health Equity Fund paying the user fees of healthcare facilities for those living under the official poverty line [25]. Consequently, some 20% of the population are covered (on a low level). At the same time, Cambodia has launched a National Social Security Fund (NSSF) to cover all formal sector workers and civil servants. In the long run, the respective services are to be expanded to the entire population.

The Vietnam Social Security (VSS) protects already some 85% of the population in case of illness [21]. Opposite to Cambodia, there is a degree of solidarity between social groups in Vietnam. It is the objective of the Government of Vietnam to protect 100% of the population by the year 2020.

The biggest single social health insurance in the world is the Jaminan Kesehatan Nasional (National Health Insurance) of Indonesia [26]. With some 157 million members it covers some 59.5% of the population. Services covered by the insurance reach from implants to MRIs. The social insurance from Indonesia has become a pattern to follow for many countries.

These three examples show that solidarity-based social protection systems are developing all over the world. Without doubt, much has still to be done, but the improvement of UHC will also have a strong impact on the demand for medical devices in these countries. Equipment and implants which are unaffordable for the individual in case of illness become a regular service component of the broad risk pool.

12.3.3 Aging Population and Urbanization

The impact of economic growth and health insurance coverage on the demand for healthcare services will be accelerated by a strong demographic [27] and epidemiological transition [28]. The traditional understanding of healthcare in low and lower-middle-income countries was that the respective population is young and suffers from infectious diseases, while the population in upper-middle- and high-income countries is comparably old with chronic-degenerative diseases. While this assumption was quite true 20 years ago, it is partly wrong today. And it will definitely be wrong within the next 30 years.

Figure 12.10 shows the proportion of population aged 60 or over in 2014 and 2050. While the first impression is a worldwide aging, the most tremendous effects are in Asia, in particular China, Thailand and Saudi Arabia. The 60+ population will require higher health expenditure, and in particular their chronic-degenerative diseases will require more diagnostic devices and implants.

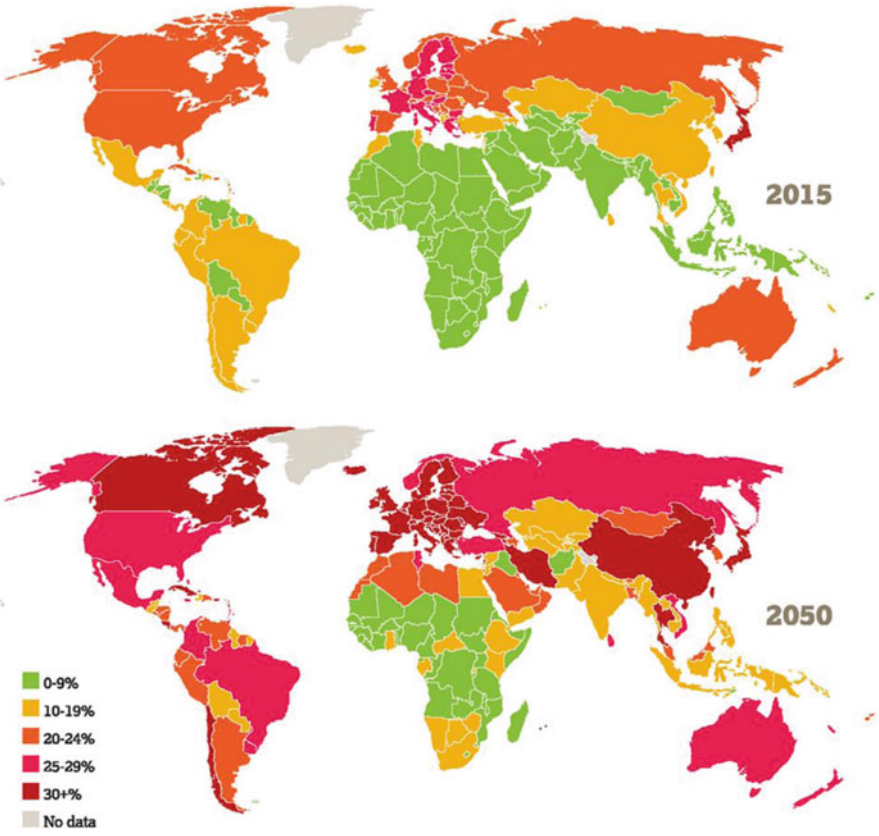

Fig. 12.10 Changes in population structure between 2015 and 2050 [29]

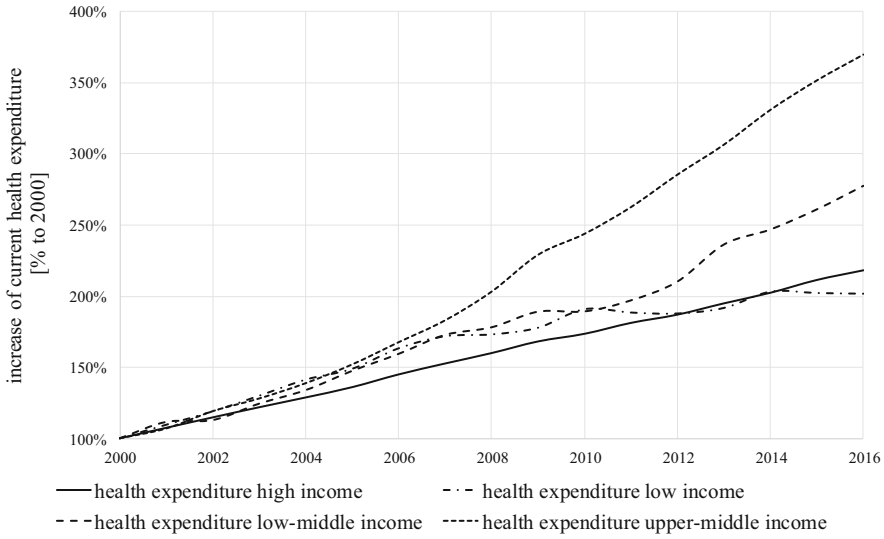

Fig. 12.11 Health expenditure increase. (Source: own, based on data of [1])

Summarizing, we can state that low and lower-middle-income countries constitute a tremendous economic potential for medical device producers. 49.2% (2017) live in low and lower-middle-income countries, while only 16.6% live in high-income countries. This great market for medical devices is constantly growing because these economies grow, more and more people share the risks of illness and the population is aging. The healthcare expenditure per capita has strongly grown (see Fig. 12.11) all over the world, and there is no reason to believe that this trend will come to an end. Instead, the category of low-income countries will disappear soon in Asia and more and more people will enjoy high-end medical devices. This market should be prepared by now.

Let us close with an allegory. German and French brands dominated the African car market until 1980. The VW Beatle, VW Bulli and Peugeot (204)—in addition to the expensive Land Rover—were omnipresent and services as well as spare parts were available in all major African towns. In the 1980, Asian car manufacturers started producing rather cheap and reliable four-wheel drive cars and conquered the African market. European producers did not realize a market chance in the segment of four-wheel drives and neglected Africa. They could have built on their quasi-monopoly—but they ignored the chance. Today, more than one million cars are sold every year in Africa but VW and Peugeot are not among the market leaders [30]. A cheap and reliable four-wheel drive launched in 1985 by these two manufacturers would have been without a serious competitor—but the chance was lost.

The analogy is obvious: European medical devices have still a high reputation in Africa and Asia. Those countries which Europeans tend to call “developing countries” are the future of our products with billions of customers, steadily increasing economic potential and increasing demand. The misjudgement of the car industry should not be repeated by European medical device producers.

Conclusion

Most people and even scientists think about high-income countries when they talk about medical technology. It is obvious that the average person is much richer in this group of countries in comparison to the average population in low-income countries. In the absence of (social) health protection and with a need to finance modern technology out-of-pocket, it is unlikely that the majority of the population of these countries will benefit from top-quality medical products within the coming years. However, this is only one side of the coin. The other side is that even very poor countries have still a minority of very rich and internationally insured potential customers. The tremendous population of these countries is aging—and by this the markets will grow accordingly. Neglecting these markets with ready-to-pay customers might be an unwise business decision today—but it will turn out to be a commercial disaster within the next decade. The emerging markets might become markets as strong as traditional western markets for health technology soon, and what are called "developing countries" today might be the new markets tomorrow. It is now time to pay attention to these markets.

Take Home Message

- Almost half of the world population lives in low and lower-middle-income countries.
- The markets for medical devices in low- and middle-income countries are steadily growing.
- There is demand for simple and cheap as well as for sophisticated devices.
- Enterprises should focus on the needs and preferences of people in low and lower-middle-income countries, get acquainted to the specifics of cultures and markets and start cooperation and joint ventures soon—otherwise they will lose these markets.

References

1. World Bank World Development Indicators (2019) The World Bank, Washington DC
2. Fleßa S (1998) Many worlds of health: a simulation of the determinants of the epidemio-logical transition in developing countries. Zeitschrift für Bevölkerungswissenschaft 23(4):459–494
3. Rosling H (2019) Factfulness. Flammarion, Paris
4. Flessa S (2002) Gesundheitsreformen in Entwicklungsländern. Eine kritische Analyse aus Sicht der kirchlichen Entwicklungshilfe, Frankfurt a.M.: Lembeck
5. World Bank (2019) World Bank Country and Lending Groups. https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups
6. World Bank Classification of Countries by Income (2019). http://datatopics.worldbank.org/world-development-indicators/stories/the-classification-of-countries-by-income.html
7. Rapid CMR Our Mission (2021) https://www.rapidcmr.com/copia-de-acerca-de-nosotros
8. WHO Global Burden of Disease (2013) http://www.who.int/healthinfo/global_burden_disease/estimates_regional/en/index.html
9. Fleßa S (2012) Internationales Gesundheitsmanagement: Effizienz im Dienst für das Leben. Oldenbourg, München

10. Credit Suisse Global Wealth Report 2018 (2019) Zürich: Credit Suisse
11. Index Mundi Gini Coefficient (2019). https://www.indexmundi.com/facts/indicators/SI.POV.GINI/rankings
12. World Bank (2013) Where have all the poor gone? Cambodia poverty assessment 2013. The World Bank, Washington
13. Mushi L, Marschall P, Fleßa S (2015) The cost of dialysis in low and middle-income countries: a systematic review. BMC Health Serv Res 15(1):1–10
14. Abu-Aisha H, Elamin S (2010) Peritoneal dialysis in Africa. Perit Dial Int 30(1):23–28
15. El Matri A, Elhassan E, Abu-Aisha H (2008) Renal replacement therapy resources in Africa. Arab J Nephrol Transplant 1(1):9–14
16. Fuchs VR (2011) Who shall live? Health, economics and social change. World Scientific, New Jersey
17. Capgemini World Wealth Report 2018 (2019) https://worldwealthreport.com/
18. Schaffmeister N, Haller F (2018) Erfolgreicher Markenaufbau in den großen Emerging Markets: Ein praxisorientierter Ratgeber für gezieltes Markenwachstum in China, Indien, Russland und Brasilien: Springer
19. Commons Emerging Countries 2013 (2019) https://commons.wikimedia.org/wiki/File:Newly_industrialized_countries_2013.svg#/media/File:Newly_industrialized_countries_2013.svg
20. Evans DB, Hsu J, Boerma T (2013) Universal health coverage and universal access. Bull World Health Organ 91:546–546A
21. Reich MR et al (2016) Moving towards universal health coverage: lessons from 11 country studies. Lancet 387(10020):811–816
22. WHO Universal Health Coverage (2019) http://www.who.int/health_financing/en/
23. Cattaneo A et al (2015) The seven sins and seven virtues of universal health coverage. Third World Resurgence 296/297:13–15
24. Adhikari A (2018) Strategic marketing issues in emerging markets. Springer
25. Wiseman V et al (2017) System-wide analysis of health financing equity in Cambodia: a study protocol. BMJ Global Health 2(1):e000153
26. Barrientos A, Hulme D (2016) Social protection for the poor and poorest: concepts, policies and politics. Springer
27. Galor O (2012) The demographic transition: causes and consequences. Cliometrica 6(1):1–28
28. Omran AR (1971) The epidemiological transition: a theory of the epidemiology of population change. Milbank Memorial Fund Quarterly 49:509–538
29. Global AgeWatch (2019) Global AgeWatch Index 2015. https://www.helpage.org/global-agewatch/population-ageing-data/population-ageing-map/
30. Motor Intelligence (2019) Africa Automotive Market—segmented by vehicle and geography—growth, trends, and forecast (2018–2023). https://www.mordorintelligence.com/industry-reports/africa-automotive-industry-outlook

Chapter 13
Ethical Aspects in Medical Devices and Ethical Committees in Clinical Trials and Regulations

Sergio Cerutti

Abstract Ethical problems are indeed relevant when dealing with medical devices, apparatuses and systems. The fundamental aspect of such devices is that they are employed for making diagnosis, therapy and rehabilitations on human subjects and therefore they manifest results in a very important field of applicative science, with direct cultural, economic, social implications and fallouts. In addition to that, it is often the case that these pieces of equipment are directly connected to the patient in various and different experimental conditions, thus creating dangerous potential situations for the patient and her/his environment conditions (macroshocks and microshocks). The role of safety and performance standards are therefore critical in order to maintain a correct and proper use of these technologies and avoiding the generation of risks and hazards for patient's health. Therefore, the "virtuous" challenge that has to be won by scientists and operators in this field is to be able to implement a system with reliable laws and rules, clear and complete technical standards, well trained clinical and technical personnel. Finally, ethical issues involve many different cultural, clinical, and managemental aspects, not necessarily confined within the concepts of modern biomedical technologies, which are of great importance and interest and which are often underestimated.

Introduction

A basic point to be remarked is that the compartments of pharmaceutical drugs (PHD) and medical devices (MD) are actually strictly regulated.

Just to provide an idea of the real impact of these compartments, it is worth to mention that the total world PHD expenditures (2019) has been of about 1200 billion US $ (about 15% of the total expenses for Health [35% USA and Canada, 28% Europe, 26% Asia, etc.], while the expenses for Medical Devices have been around 520 billion US $ [44% USA e Canada, 29% Europa, 20 Asia, etc.].

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Conversely, the number of patents for MD has had a strong increasing in the last years and reached the quote of 60,000, compared to a modest increment in the area of PHDs. Therefore, strong developments are foreseen in the future for the MD compartment in respect to PHD compartment, at least for the next expected years.

The present chapter describes the Ethical Issues with the current Regulations, in particular referring to the MD compartment. As it is well known, on 2017, the new Regulation on MD's replaced the Directive on the same topic: a 3-year term was granted for a gradual adaptation to the new document and another year was given for the 2019–2021 epidemy. Therefore, the deadline for a mandatory application of it has been fixed on May 26th, 2021. Analogously, the deadline for a mandatory application of in vitro Diagnostics Regulation (IVDR) has been fixed for May 26th, 2022. As for a coherent choice from the Author of this section, the Italian situation is mainly analysed: it is obviously inserted into the frame of EU legislation and relevant Regulations. Therefore, while some considerations will be referred to the Italian situation only, most of the rules do have a clear European perspective. These aspects will be clarified within the text.

13.1 Clinical Trials for Medicinal Products (Pharmaceutical Drugs)

The fundamental *ethical principles* to which the studies on clinical trials referred to PHD must conform, have an origin from Helsinki declaration [1], Oviedo Convention [2], Guidelines of EMA for Clinical Trials [3] and from the requirements of the international standards of **Good Laboratory Practice (GLP)**, **Good Clinical Practice (GCP)** guidelines and **Good Manufacturing Practice (GMP)** guidelines [4]. These rules and prescriptions constitute fundamental tools for implementing that process which incorporates established ethical and scientific quality standards for the design, conduct, recording and reporting of **clinical research involving the participation of human subjects** and aims at maintaining data or goods resulting from such a scientific research, in general, at a high level of quality standards.

Good laboratory practice (**GLP**) is intended to ensure the trustworthiness of laboratory data and regulates the processes and conditions under which clinical and non-clinical research is conducted. GLP also governs how these research facilities should be maintained [Directives 79/831 CE, 99/11 CE and 99/12 CE] [5]. Good clinical practice (**GCP**) guidelines are instead dictated by the International Conference on Harmonization (**ICH**). The ICH GCP governs the ethical and scientific quality of *clinical trials.* Hence, the ICH GCP covers topics such as the study design, methodology, and data reporting related to clinical trials [ICH E6 (R2) Good clinical practice] [6]. Finally, **GMP** regulates the design, monitoring, and control of manufacturing processes and facilities. GMP compliance, for example, ensures the identity, strength, quality, and purity of PHD products and it is designed to minimise the risks involved in any pharmaceutical production that cannot be eliminated

through testing the final product (Regulation No. 1252/2014 and Directive 03/94/EC, applying to active substances and medicines for human use, World Health Organization) [7].

The European Medicines Agency (EMA) relies on the results of clinical trials carried out by pharmaceutical companies to reach its opinions on the authorisation of medicines. Although the authorisation of clinical trials occurs at Member State level, the Agency plays a key role in ensuring that the standards of good clinical practice (GCP) are applied across the European Economic Area (EEA) in cooperation with the Member States. It also manages a database of clinical trials carried out in the European Union.

GMP Standards have been adopted by European Union (EU) and acknowledged inside national regulations. In particular, Directive 2001/20/EU of the European Parliament on the approximation of the laws, regulations and administrative provisions of the Member States is related to the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for human use. Further, Directive 2005/28/EC deals with the Good Clinical Practice, regarding how to conduct clinical trials of medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

Another Directive (2001/83/EU and successive updates) is relative to a Codex concerning PHD for human use, while Directive 2003/94/EU concerns Good Manufacturer Practice relative to PHDs for human use as well as to experimental PHDs for human use. Finally, Regulations EU 536/2014 deal with Clinical Trials in Humans and have been finally recognised with updates on 16/12/2014.

The above-mentioned Directive 2001/20/EU defines as "clinical trial" "any study on humans with the aim to discover or verify clinical, pharmacological or other pharmacodynamical effects of one or more experimental PHDs and/or to single out any adverse reaction to one or more experimental PHDs, and/or to study their assimilation, distribution, metabolism and wash-out, with the purpose to verify the safety and/or performance, as well as other elements of scientific character or not". This definition includes clinical trials carried on in one or more centres in Europe (clause 2, comma 1, letter a). Such trials are defined "*interventional*", in respect to "*observational*". Figure 13.1 illustrates the very long procedure which stays behind an approval of a new pharmaceutical drug.

The steps to be fulfilled are:

Pre-Clinical Test (around 3 years duration): Such a duration is estimated after a preliminary and initial period of testing new molecules, compounds or other chemical substances (around 3–3.5 years duration). That is about 6.5 years in total, as indicated in the first block of Fig. 13.1.

Such tests must evaluate the safety of the active principle (toxicity), its behaviour after the administration, in terms of absorption, distribution, metabolism, elimination (ADME) and pharmacokinetics (PK). During this phase, the drug is produced on pilot scale, respecting Good Laboratory Practice (GLP) Standards.

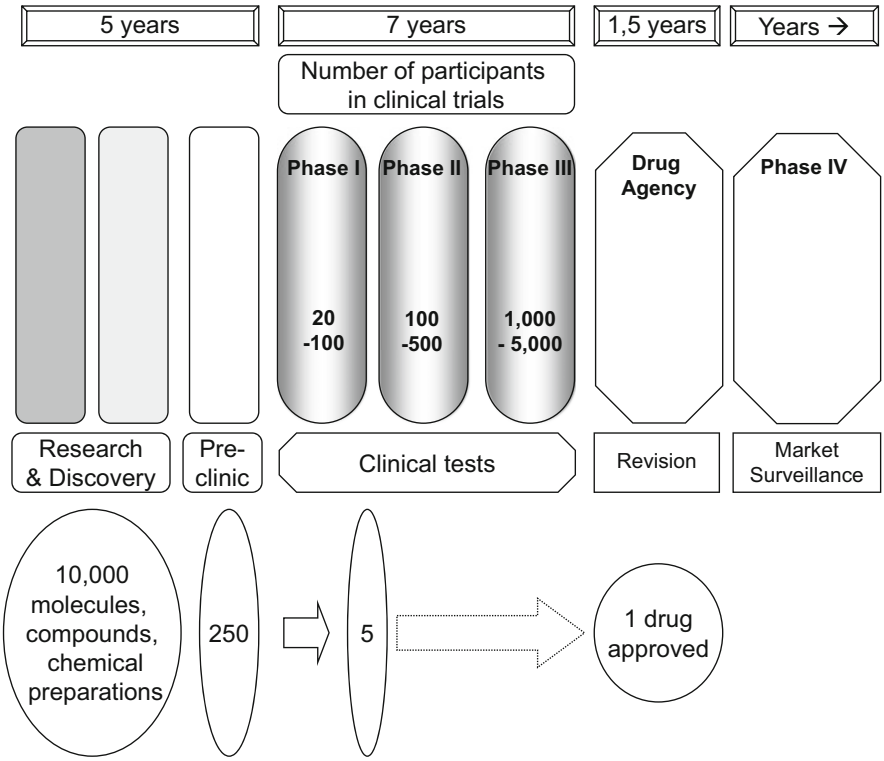

Fig. 13.1 The articulated, complex and very long procedure for the registration of a new pharmaceutical drug at EMA (European Medicines Agency)

Clinical Trials (7 Years)

The second block depicts the so-called *Clinical Trials* and are usually carried out in three main phases (Phase I, II, III). Every phase approaches different aspects and the outcome of every study phase is important to decide whether the experimentation of the new drug in a determined phase could proceed to the successive one. It is necessary to check the different phases of clinical development in order to guarantee the safety and rights of the people involved into the clinical studies, the data reliability and the compliance with the GCP Standards.

Phase I

Phase I studies are dedicated to the analysis of the **safety and tolerability profiles** of the product and generally are carried out on human healthy volunteers. The decision to pass to Phase II is taken in consideration of the obtained results in Phase I, during which sufficient information shall be collected on pharmacokinetics and in which the drug must have demonstrated to have reached a good safety and tolerability levels.

Phase II

During Phase II, the drug is given to a selected group of patients (generally 100–300 people). The aim of these studies is to determine whether the new drug is really **effective for the treatment** of the pathology. Further, the dose and frequency of delivery must be determined to obtain the better efficacy with the lower possible number of adverse events. At the end of Phase II, the efficacy data obtained, the safety profile and adverse events must be examined and properly considered at the aim of deciding whether the drug could pass on to Phase III of clinical trials and to process the best design for the successive studies.

Phase III

Phase III studies are programmed to confirm the **drug efficacy and to monitor the adverse events over longer time span**: in fact, they base on the observation of a greater number of patients (around 1000–3000 patients of different geographic areas) and for a longer period of time (in average 2–3 years, depending upon the type of therapy and pathology. Once Phase III studies are completed and if the results have been significantly confirmed, proper documentation on drug efficacy and safety is sent to regulatory Authorities in order to receive the "Authorisation to the Market Admission (AMA)".

Approval of Regulatory Authority and Marketing (1–2 Years)

The approval of a drug from a regulatory Authority is often a rather long process which requires about 1 year for the revision of all the documentation and the delivery of a final decision. After the Authorisation to the Market Admission (AMA), the following step is to launch the product into the market, involving marketing departments which must produce a detailed market study, a communication plan, a registered mark and a suitable training plan for the personnel who will manage the product promotion.

Post-market Surveillance (Phase IV)

After the drug is approved by the regulatory authorities, it is necessary to execute the so-called **pharmaco-vigilance**, i.e. to continue to monitor the safety, by collecting information about drug **adverse reactions** from different sources, including spontaneous warnings. Such an activity is a law requirement and is fundamental to guarantee public health, as it is fundamental to confirm the safety data collected during clinical trials on the real patient's population and over a long term. Among the pharmaco-vigilance activities there is the continuous monitoring of risk/benefit ratio in order to guarantee that the advantages of the therapy with the product are always greater than the risks originated from possible side effects.

It is worth to remark the fact that generally the whole procedure starts with the analysis of a huge number (even *10,000*) of initial molecules or compounds and finishes (hopefully) with the official approval of *one* drug! And that happens 15 years after the first step, if no emergential procedure is decided to be put into practice!

Observational Studies on Drugs

As illustrated by AIFA, the Italian Agency for Drugs, inside the Guidelines for Observational Studies on Drugs, it is established that the observational studies on drugs are particularly important for the evaluation of the safety profile in the normal use conditions and over a great number of patients, to go deep into the efficacy of the clinical practice, the pertinency of the prescriptions and the evaluations of "pharma-economic type". A statement of that kind is also present in other European legislations and therefore it is here presented as an example of a more general case.

Due to their characteristics, observational studies do not imply additional risks to the patients to whom the best conditions of clinical assistance are offered. Consequently, they require differentiated procedures in respect to what is required in the experimental clinical studies.

Particular caution is required in order to avoid that a clinical trial is presented as an observational study.

To this purpose, it is important to note that drug studies must satisfy the following conditions in order to be considered non-experimental:

1. The drug must be provisioned according to the use indications, as in the Authorisation to the Market Admission in Italy (or in another European Country).
2. The prescription of the drug must be part of the clinical practice.
3. The decision to prescribe a drug to the single patient must be independent from the one to include the patient in the study.
4. Diagnostic and valutative procedures must comply with the current clinical practice.

It is necessary that Ethical Committees are informed on the development of these studies in the health structure or on their territorial jurisdiction. It is also necessary that, according to the proposed observational study, Ethical Committees always receive a notice of the study or a formal request for the formulation of an opinion.

13.2 Clinical Trials on Medical Devices and In Vitro Diagnostics Medical Devices

Actually (2021), the entire sections of MD and IVD-MD are under the umbrella of two Regulations, which have the force of laws in Europe. One on MD and the other one on IVD-MD (see also Fig. 13.2).

On May 2021, the EU MDR has replaced the EU's current Medical Device Directive (93/42/EEC) and Directive on Active Implantable Medical Devices (90/385/EEC). On May 2022 the EU IVD-MD—Regulations will replace the EU current in vitro Diagnostic Medical Devices Directive (98/79/EEC).

These two new Regulations were adopted on 5 April 2017, and they entered into force on 25 May 2017. These have replaced the existing Directives, as indicated.

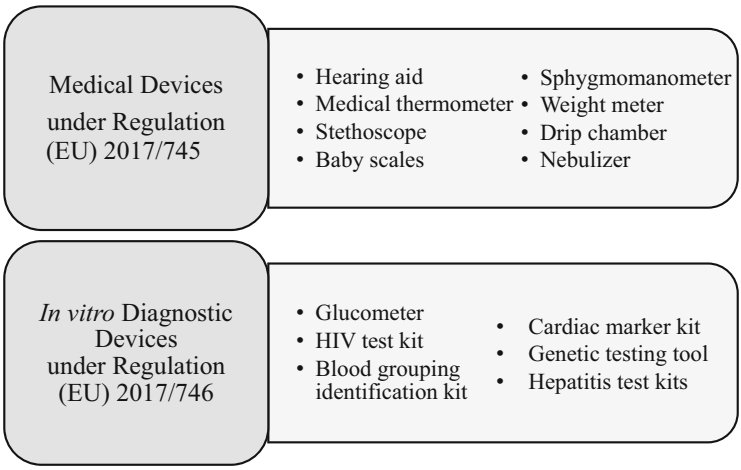

Fig. 13.2 Examples of equipment covered by the two Regulations on Medical Devices (MDR) and in vitro Diagnostics Medical Devices (IVD-MD)

Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on **medical devices**, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on **in vitro diagnostic medical devices** and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

The new rules will only apply after a transitional period. Namely, 3 years after entry into force for the Regulation on medical devices (**Spring 2020)** and later on postponed to **2021** for the COVID epidemy) and 5 years after entry into force (**Spring 2022**) for the Regulation on in vitro diagnostic medical devices.

The need for a re-formulation of these **Regulations** came from serious incidents connected to deficits in medical devices (*silicon-gel mammary prostheses, metal-to-metal hip prostheses, etc.*) happened in the last decades and which influenced a lot even European public opinion. The former legislation, based upon **Directives**, demonstrated to be unable to avoid these incidents. This underlines the importance of the ethical issue about the full compliance to all safety and risk requirements.

13.2.1 The New Regulations on MD in a Nutshell

The new Regulations contain a series of extremely important improvements to modernise the current system. Among them are:

- **stricter ex-ante control for high-risk devices** via a new pre-market scrutiny mechanism with the involvement of a pool of experts at EU level

- the **reinforcement of the criteria for designation and processes for oversight of Notified Bodies**
- **the inclusion of certain aesthetic devices** which present the same characteristics and risk profile as analogous medical devices under the scope of these Regulations
- the introduction of a **new risk classification system for in vitro diagnostic medical devices** in line with international guidance
- **improved transparency** through the establishment of a comprehensive EU database on medical devices and of a device traceability system based on Unique Device Identification
- the **introduction of an "implant card"** containing information about implanted medical devices for a patient
- the **reinforcement of the rules on clinical evidence**, including an EU-wide coordinated procedure for authorisation of multi-centre clinical investigations
- the **strengthening of post-market surveillance** requirements for manufacturers
- **improved coordination mechanisms** between EU countries in the fields of vigilance and market surveillance

The stages of CE mark procedure for Medical Devices are:

1. Device classification
2. Compliance check of General Safety and Performance Requirements (SPRs)
3. Delivery of CE Mark of the product

For a detailed analysis of the basic philosophy, the definitions and international Regulations for Medical Devices and in vitro Diagnostics Medical Devices, see Chap. 4 of this book.

1. The *Classification* is the first action which has to be made by the manufacturer in order to single out the device class and to adopt the relevant mark procedures.
2. Any medical device must comply with the so-called General Safety and Performance Requirements (GSPRs'). These requirements, which are indicated in the EU Regulations, are mandatory for both the device and its production system. The objective is that the devices must be designed and produced in such a way that their use does not threaten patient's clinical state, nor user's or third party's safety and health, when they are used under the conditions and for the expected aims. The possible risks must be at an acceptable level, taking into account the benefits brought to the patient and being compatible with a high level of health and safety protection. That means that, in order to produce a medical device, the manufacturer must demonstrate that not only its product, but also the manufacturing process in its different aspects are in agreement with these requirements (project, fabrication, controls, etc.).

Compliance with the 'General Safety and Performance Requirements (GSPRs)' is a cornerstone in establishing conformity with the recently published MDR. The GSPRs are detailed in Annex I of the MDR. The GSPRs have replaced the Essential Requirements (ERs) found in Annex I of each of the former Medical Device

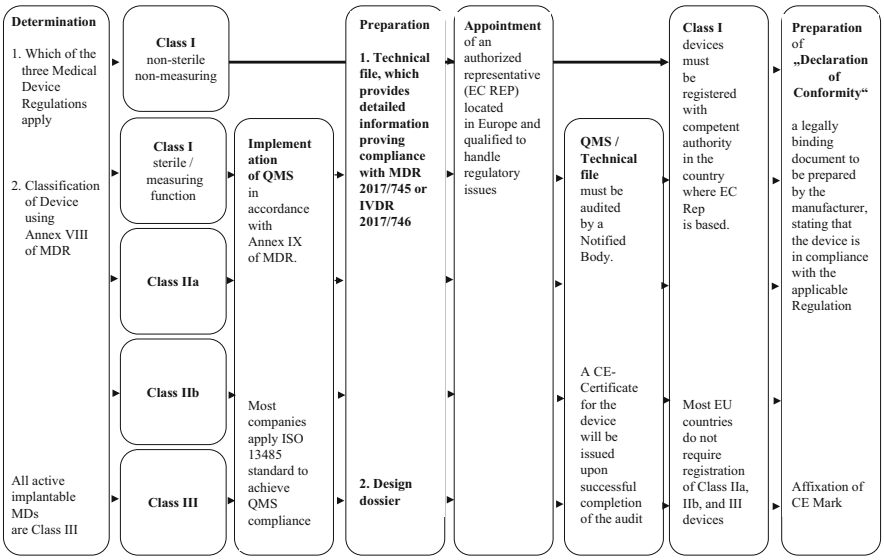

Fig. 13.3 Overall procedure for obtaining the CE Mark on a medical device. *QMS:* Quality Management System, *MDR:* Medical Devices Regulation, *IVDR:* in vitro Diagnostic Regulation

Directive (MDD) and former Active Implantable Medical Device Directive (AIMDD).

The basic philosophy is that the higher the risk of the device, the greater shall be the guarantees for safety for the device production provided by the manufacturer. The entire procedure for obtaining a CE Mark on a device is depicted in Fig. 13.3, starting from the initial step of device classification, up to the final step of affixing the CE Mark on the device itself.

For Class I equipment, the manufacturer could mark the product and put it into the market after writing a "CE declaration of conformity" to the General Safety and Performance Requirements. Through such a document, the manufacturer guarantees and declares that his products fulfill the Regulation requirements. However, the company shall have available all the technical documentation suitable to demonstrate the safety of the produced product. The "CE conformity declaration" is the simplest procedure of the CE mark. It deals with a simply declaration of assumption of responsability, without the intervention of a Notified Body.

13.3 Regulation (EU) No. 2017/745

As a mere example of application, the EU Regulation 2017/745 of the European Parliament and of the Council of 5 April 2017 concerning medical devices (hereinafter, the "MDR") repealing Directive 90/385/EEC (hereinafter, the "AIMDD") and

Directive 93/42/EEC (hereinafter, the "MDD"), is here reported. Such a regulation entered into force on 25 May 2017. As stated by EU Regulation no. 2020/561 of 23 April 2020, the MDR will come into force from 26 May 2021 on.

The MDR regulates:

- Medical devices for human use and their accessories (ref. art. 1, p.1 of the MDR);
- Device not placed on the market but used in the context of a commercial activity to provide a diagnostic or therapeutic service through information delivered and stored by services companies or other means of communication (ref. art. 6 of the MDR);
- Products that are not intended for medical use and listed in Annex XVI (ref. art. 1, p. 2 and Annex XVI of the MDR).

From May 27, 2024, only medical devices conforming to the MDR with a valid EU certificate of conformity issued in accordance with the MDR may be placed on the market.

13.3.1 Classification of Devices and Conformity Assessment Procedures

The Devices are divided into four risk classes I, IIA, IIB, III according to their intended use and the risks involved.

The classification is carried out by the Manufacturer according to the criteria of Annex VIII of the MDR (ref. art. 51 of the MDR).

Before placing a device on the market or in service, the manufacturer must assess the conformity of the device in accordance with the applicable conformity assessment procedures set out in Annexes IX to XI (ref. art. 52 of the MDR).

The conformity assessment procedures applicable to each class of risk are set out Table 13.1.

If the conformity assessment procedure requires the intervention of a Notified Body, the Manufacturer (or its Authorised Representative) submits an Application for Certification to a designated Notified Body of its choice (see Table 13.2).

13.4 Key Aspects of the New Medical Device Regulation (MDR)

- It introduces new classification rules and modifies some of the former MDD rules, making the classification criteria more stringent (ref. Annex XVIII of the MDR).
- It has four risk classes: I, IIA, IIB and III (Active implantable medical devices are in Class III).

Table 13.1 Conformity assessment procedures applicable to each MD class of risk

Device class	Conformity assessment procedure (MDR Annexes)	Intervention of the notified body
I (non-sterile, without measuring function, nonreusable surgical instrument)	Declaration of conformity (Annex IV)	Not required
I sterile (IS) I with measurement function (IM) I Reusable surgical instrument (IR)	– Annex IX—chapter I *or* – Annex XI—part A	Yes, the intervention of the Notified Body is limited respectively to:-"aspects relating to establishing, securing and maintaining sterile conditions";—aspects relating to the conformity of the Device with the metrological requirements;—aspects relating to the reuse of the Device (cleaning, disinfection, sterilisation, maintenance and functional testing and the related instructions for use)
IIa	– Annex IX—chapter I *or* – Annex XI—Part A *or* – Annex XI—Part B	Yes
IIb (non-implantable)	– Annexo IX—chapter I *or* – Annex X combined with Annex XI—Part A *or* – Annex X combined with Annex XI—Part B	Yes
IIb implantable[a] III	– Annex IX chapter II combined with Annex IX—chapter I *or* – Annex X combined with Annex XI—Part A *or* – Annex X combined with Annex XI—Part B	Yes

[a]Annex IX—Chapter II does not apply to the following implantable Devices: sutures, staples, dental fillings, dental braces, tooth crowns, screws, wedges, plates, wires, pins, clips or connectors

- It introduces economic operators (Manufacturer, Authorised Representative, Importer and Distributor) and defines their specific obligations.
- It introduces the need for the Manufacturer to have financial coverage and a person responsible for compliance.
- It strengthens the need for the Manufacturer to have: a risk management system; a post-market surveillance system; a system for reporting incidents.

Table 13.2 The conformity assessment procedures as set out in Annexes IX–XI. (*QMS:* Quality Management System)

MDR Annex		MDR conformity assessment procedure		MDR certificate	Corresponding MDD/AIMDD Annex
Annex IX	*Annex IX chapter II*	Device design assessment	Assessment of the Device technical documentation	EU technical documentation assessment certificate	Annex II.4
	Annex IX chapter I	Assessment of the quality system (complete)	Assessment of the complete quality system applied to all phases—design, manufacture and final control of the product, with verification of the technical documentation of the Devices covered by this QMS	EU quality management system certificate	Annex II except 4
Annex X		Product assessment	Assessment of the technical documentation of the Type and Performance of tests on a representative example of a given production (type verification)	EU type-examination certificate	Annex III
Annex XI—part A		Assessment of the quality system production quality assurance)	Assessment of the quality system applied to the manufacturing phase of the product, including verification of the technical documentation of the Devices covered by this QMS	EU quality assurance certificate	Annex V
Annex XI—part B		Product assessment (related to production)	Assessment of the technical documentation of the Device and Performance of tests on each individual product	EU product verification certificate	Annex IV (verification of each Device)

- It strengthens the need for the Manufacturer to demonstrate compliance with clinical data.
- It introduces the drafting of specific documents by the Manufacturer: Safety and clinical performance summary for Class III Devices and Implantable Devices, Post-market surveillance report for Class I Devices and Periodic safety update

report for Class IIA, IIB and III Devices; Trend reporting; Card for patients with implantable devices.
- It strengthens the concept of traceability of devices with the creation of the UDI system.
- It strengthens the use of EUDAMED (European Database on Medical Devices) for the collection of Device information in a single European database.
- It eliminates conformity assessment procedures based on product quality assurance (Annex VI of the MDD) and statistical product verification (Annex IV of the MDD with sampling).

13.4.1 Quality Management System (QMS)

The conformity of Medical Devices and in vitro Diagnostic Medical Devices according to the European Union Regulations or (previously) Directives must be assessed before sales are permitted. One of the major requirements to prove conformity is the implementation of the Quality Management System (QMS) according ISO 9001 (general rules) and/or ISO 13485 (MD's) (2016) and ISO 14971 (Risk Management in MD's) (2019). Even if the EU Regulations do not mandate certification to ISO 9001 and/or ISO 13485, the preferred method to prove compliance to such standards is to seek its official certification which is issued by certifying organizations (Registrars or Notified Bodies). A very careful assessment of the company's Quality Management System by the Notified Body, together with the review of the required Technical Documentation, is a major element which the Notified Body takes into account to issue the certificate of conformity to the company product(s).

13.5 Ethical Aspects and Ethical Committees

The Ethical Committee for clinical trials of medicinal products and of Medical Devices is an independent body which has the responsibility to guarantee the protection of rights, safety, and well-being of subjects in the trial and to provide public warranties of such a protection. The Committee can be established inside one or more public health structures (or comparable others, such as hospitals), in conformity to the applicable discipline. Further, the Ethical Committee is formed, in agreement with the regional standards, inside the in-charge regional administration.

Ethical Committees can also have a consultive function in relation to ethical issues connected with the scientific and welfare activities. The purpose is to guarantee the protection and foster human subjects values, if these functions have not already been attributed to other specific organisms. Further, Ethical Committees may propose initiatives of training the health operators, in relation to bioethics matters.

As a European reference, Directive 2001/20/CE may be mentioned which is relative to the application of Good Manufacturing Practices in the execution of drug clinical experimentation in clinical use. In Italy, the D.M. 12th May 2006 has established the minimal requirements for the establishment, the organisation and the functioning of Ethical Committees. Finally, Ethical Committees are responsible:

- to make the revision and to express an opinion on the protocol under study.
- to evaluate the proposed significant amendments and to convey an opinion.
- to verify the identity of experimenters, of structures, of materials and methods to be employed.
- to obtain and support the informed consent of the participants to the clinical study.
- to make periodical re-evaluations of approved studies.

13.5.1 Ethical, Scientific and Methodological Evaluation of Clinical Studies

Ethical, scientific and methodological evaluation of clinical studies has a reference which is expressed by the previously mentioned Directive 2001/20/CE, and by Helsinki declaration, Oviedo convention, GCP requirements and by the updated guidelines of EMA, regarding the evaluation of efficacy of clinical trials.

Ethical problems are becoming more and more important and pervasive in all human activities in healthcare. As far as scientific research is involved, there is also an "utilitarian" aspect to be considered: no scientific journal publishes now a research, an experimental or a developmental paper implying human subjects or animals without the approval of an Ethical Committee.

It is clear that the regulatory aspects of MD and IVD-MD are fully covered by proper EU Laws (Regulations) as well as by proper Technical Standards issued by qualified Committees of IEC and ISO. Most of these standards, related to the topic of MD and IVD-MD are also incorporated into European technical legislation as Mandate Standards. It has not been always managed in this way. Some decades have been required to reach such a rational organisation of EU Laws and acknowledged Technical Standards. It was necessary to make a long journey to reach this point, also passing from the "regime" of *EU Directives* to the one of *EU Regulations* on 2017.

Taking into account ethical aspects we may reasonably start from the ten points of the *Nuremberg Code.* This Code is constituted by a set of research ethical principles for human experimentation created as a result of the Nuremberg trials against members of German Nazi party, responsible for a variety of war crimes during the World War II. In particular, the so-called *Doctors' Trial* gave rise to the delivery of a Code (in 1947) which included innovative principles such as:

- Informed consent
- Absence of coercion
- Properly formulated scientific experimentation
- Beneficence towards passive participants involved in the experiment.

This concept is mainly based on the *Hippocratic Oath*, which was interpreted as endorsing the experimental approach to medicine while protecting the patient.

The ten points which constitute the Code are:

1. The **voluntary**, **well-informed**, **understanding consent** of the human subject in a **full legal capacity is required**.
2. The experiment should aim at **positive results** for the society that cannot be procured in some other way.
3. It should be based on **previous knowledge** (e.g. an expectation derived from animal and pre-clinical trials) that justifies the experiment.
4. The experiment should be set up in a way that **avoids unnecessary physical and mental suffering** and injuries to the passive participants (human or animal).
5. It should not be conducted when there is any reason to believe that it implies a **risk of death or disabling injury**.
6. The **risks** of the experiment should be in **proportion** to (that is, not exceed) the **expected humanitarian benefits**.
7. Preparations and facilities must be provided that adequately **protect the subjects against the experiment's risks**.
8. **The staff** who conduct or take part in the experiment must be **fully trained and scientifically qualified**.
9. The human subjects must be free to immediately **quit the experiment** at any point when they feel physically or mentally unable to go on.
10. Likewise, the medical staff must **stop the experiment** at any point when they observe that continuation would be dangerous.

13.5.2 European Regulation on Clinical Trials: Towards the Harmonisation of Standards on Clinical Trials

Regulation n. 536/2014 dated on 16th April 2014, on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC has entered into force in 2019.

The Regulation will ensure a greater level of harmonisation of the rules for conducting clinical trials throughout the EU. It introduces an authorisation procedure based on a single submission via a single EU portal, an assessment procedure leading to a single decision, rules on the protection of subjects and informed consent, and transparency requirements.

It will also make it easier for pharmaceutical companies to conduct multinational clinical trials, which should increase the number of studies conducted within the EU. The general principle is outlined in Art. 3 of the above-mentioned regulation.

A clinical trial may be conducted only if: (a) the rights, safety, dignity and well-being of subjects are protected and prevail over all other interests; and (b) it is designed to generate reliable and robust data.

To improve data transparency from clinical trials, a European public and accessible databank of detailed abstracts (including final relations) will be available once a final decision is taken for the market submission or when an authorisation is rejected.

No application disclosure will be anymore accepted among European Member States. The strengthpoints are: (1) unique evaluation of a clinical trial, shared by all the Member States , (2) unique portal and European database directly managed by EMA and (3) unique access point for the documentation delivery and access.

Finally, it is worth to remember that also Regulation EU 2016/679, 27th April 2016, "General Data Protection-GDPR, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data", is mandatorily active from 25th May 2018. Particular attention is dedicated to *Health Data* (anagrafic, from medical record, biometric, genetic). A DPO (Data Protection Officer) is also foreseen who could be involved within 72 h from the possible violation to be notified to Privacy Authority. There is also mention to Accountability Commitments (at various levels) in the collection of these personal data.

For a complete implementation of DGPR, at least in Italy, we will have a National Law + Advice from Italian Privacy Authority.

It is worth to remember that an Ethical Committee must be interdisciplinary, i.e. is constituted by different experts from various areas. As an example, the Ethical Committee of the European Institute of Oncology and the Cardiological Institute in Milan is constituted by experts in the following areas or specialities:

Cardiosurgery, Pharmacology, Bioethics, Profession in Health, Biomedical Engineering, Genetics, Surgery, Biostatistics, Volunteering and patient safeguard, Clinical Oncology, Clinical Cardiology, Legal and insurance, Pharmaregulation, Pharmacy management, General Medicine, Pediatry.

Conclusion

The area of **Pharmaceutical Drugs** and **Medical Devices** is very complex, but has the characteristics of being *ruled* by *European Laws (Regulations)* and *Technical Standards*. Appropriate skills are required to correctly manage the various processes involved. The various and different skills of the involved stakeholders must be integrated with the adequate management actions.

On many occasions, it is the whole system that is inefficient and not very available to innovation. As an example, a major effort should be dedicated to improve its efficiency and efficacy through innovative measures relative to electronic informed consent, unified standards for the EHR, greater participation of the patient with perception of better control over her/his health situation and, finally, greater cooperation between trial researchers and treating physicians.

An important reference point, according to the official GCP document, is that two paper documents are still required. One for the patient and one for the clinical structure. Are we ready to move to fully computerised solutions? There are certainly

some regulatory, legal, insurance aspects and constraints, and others which still require documents in paper.

The developments of ICT-related techniques on the one hand and the considerable sociological change that will occur in the coming years (increase in the elderly population, increase in diseases linked to chronicity, different composition of the Italian/European population, lower activity in the hospital and greater activity on the territory and in the home environment, etc.) will be a challenge that must be won with a visionary, efficient and effective concept. It must involve all the actors on the scene of the Health System in order to create well-being for the entire population, not only **to increase the years of life**, but *improve life in living years* (QoL).

Regarding ethical Issues and the role of the Ethical Committees, it is fundamental to preliminarily think of the Patient to provide him with a "*Simple, Explicit, Free, Personal, Conscious and Manifest, Preventive, Specific and Confidential report*" and to represent *her/his interests* in front of very powerful stakeholders (companies, researchers, representatives of healthcare systems and political decision makers).

Among the major problems encountered into the field, it is important to remark the following aspects:

- Compromise to be reached between scientific development and benefit to the patient.
- Compromise to be reached between privacy and security problems and the advantage of data-sharing.
- Ethical and methodological aspects of Trials vs Placebo.
- Informed Consent [the e-consent is actually strongly encouraged]
- "Precision Medicine" vs "Protocol-Based Medicine" (!)
- Ethical dilemmas (efficient cost/benefit analysis before choosing a therapeutical procedure)
- To think preliminarily of the Patient; to find optimal tools of analysis: it was quoted that Google is better than WHO for the prediction of flu epidemies (!!??)
- Fundamental message: ethical problems must NOT be felt like a constraint, rather as a developmental motor to innovation (devices and instruments built according to a "people-oriented" paradigm.

The final objective is to be able to fulfill an "**Integral Ecology**", starting from "*Laudato si', sulla Cura della Casa Comune*" (*Praise Be to You - on Care for our Common Home*), expressed in the second Encyclical letter of Pope Francis, 2015 [8].

There, the concept of "Integral Ethics" is introduced: a triad Man, Animal, Nature has to be maintained for the well-being of All. Finally, there is a "Unique Tale" on the origin of Universe and hence of our planet. There is only one genealogic tree which gathers together all the living beings (including Man). The first Book that God wrote were not the Holy Texts, but the Cosmos.

Take Home Message

- Ethics is a very relevant issue when dealing with pharmaceutical drugs, medical devices, apparatuses and systems. Like drugs, the field of medical devices is strictly regulated by Laws (Regulations) and Technical Standards. Appropriate skills are required to correctly manage the various processes involved.
- When dealing with the development of medical devices, the right compromise must be reached between scientific and technological development and benefit to the patient. In addition, the conciliation between patient's privacy and security and the advantage of data-sharing should be considered.
- The evaluation of the cost/benefit ratio for the selection of a therapeutical procedure, including a risk analysis, should also be considered as an ethical aspect.
- Ethical considerations are not a constraint, but should be considered as a developmental motor for innovation. Medical devices and instruments must be built following a "people-oriented" paradigm.

References

1. World Medical Association (2013) Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 310:2191–2194. https://doi.org/10.1001/jama.2013.281053
2. Council of Europe (1997) Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: convention on human rights and biomedicine, ETS No. 164—Oviedo, 4 Mar 1997
3. European Commission and Council (2014) Clinical Trial Regulation (Regulation (EU) No 536/2014) on clinical trials on medicinal products for human use
4. Understanding the Regulations: GLP vs GCP vs GMP, Enago Academy (website), Last accessed June 2021
5. Medicines and Healthcare products Regulatory Agency (updated in 2021) Guidance on Good Laboratory Practice (GLP) for safety tests on chemicals
6. Otte A, Maier-Lenz H, Dierckx RA (2005) Good clinical practice: historical background and key aspects. Nuclear Med Comm 26:563–574
7. Patel KT, Chotai N (2008) Pharmaceutical GMP: past, present, and future—a review. Pharmazie 63:251–255
8. Pope Francis (2015) Second Encyclical Letter "Laudato si', on care for our common home"

Chapter 14
Medical Devices in Healthcare: Where We Are and Where We Are Going

Carlo Boccato, Sergio Cerutti, and Joerg Vienken

If I had an hour to solve a problem and my life depended on the solution, I would spend 55 minutes determining the proper question to ask. For, once I know the proper question, I could solve the problem in less than 5 minutes.
(Albert Einstein)

A systems perspective can minimize the mess; many of today's problems are because of yesterday's solutions.
(Dr. Irene Akua Agyepong, Ghana Health Service—Ministry of Health, Ghana, 2009)

Abstract In this chapter, as conclusive thoughts, the editors of the book give an overview of the problems and opportunities of present healthcare systems.

Healthcare is recognised as a very complex scenario, with several critical aspects that may be difficult to manage. There are also many opportunities for physicians, bioengineers and managers to improve the quality and value of care. Technology has obviously an important role in boosting these improvement chances. For this reason, a summary of the most promising innovations is given.

The followed approach to address the complexity of the healthcare system is to adopt a holistic systems' approach. The task to ask questions with focus on multidisciplinary methodology is taken by experienced contributing authors. A summary table guides the reader to these questions about topics like value, sustainability and innovation and answers provided in the appropriate chapters.

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Our final considerations will start with these two citations shown above. They describe the attitude followed by the authors when writing this book: asking questions and finding answers whilst taking a close look on the application of medical devices as a system approach. In the following, we will summarise some of our considerations and try to venture a prognosis on possible future properties and functions of innovative medical devices.

A Complex and Promising Scenario

The present panorama of the healthcare system is characterised by different actors, their mutual interactions as well as strengths, weaknesses, opportunities and threats (SWOT-analysis) of medical devices. By this means we attempted to give some orientation to navigate the complex realm of medical device technology and its application, whilst also considering the special strategic role of medical device manufacturers.

Factors to be considered are:

- Assessment of the economic and sociocultural environment of medical device application, including dangers, risks and chances.
- Analysis of financial and human resources, as well as technological capabilities in the realm of medical devices.
- Determination of key indicators to describe quality and performance of both medical devices and treatment modes in order to achieve the success of a therapy.
- Commitment to implement measures to guarantee socioeconomic accomplishments.

With the mind-map shown in Fig. 14.1, even if not fully exhaustive, this complex scenario can be closely depicted. The map also highlights the impact of medical device technology on ambulant and clinical accomplishments of healthcare systems, and touches aspects we would like to share with the respected reader.[1]

Major contributions with impact on healthcare come from various stakeholders which explain the need for harmonisation among different competing targets and among the different national and international legal prescriptions. The *Kissik's iron triangle* [1] underlines e.g. that delivering care quality, allowing general access to care for all in need whilst keeping the cost within a sustainable level are such conflicting objectives in need for harmonisation.

Following WHO [2], and reproposing a model from T. Tanahashi [3], there is an important potential for the improvement of healthcare systems. This can be achieved by addressing specific targets for both performance and quality of medical treatment as well as ensuring services for the populations. The present performance gaps towards the universal delivery of an effective and affordable coverage of health

[1] This map focus on the role of technology. Of course, the presence of the different actors like healthcare professionals, managers and policy makers plays a major role. The involvement of the lay carers should also not be neglected. The contribution of this people is not mentioned in the Fig. 14.1, but should be considered also in respect to their important interaction with the technology itself.

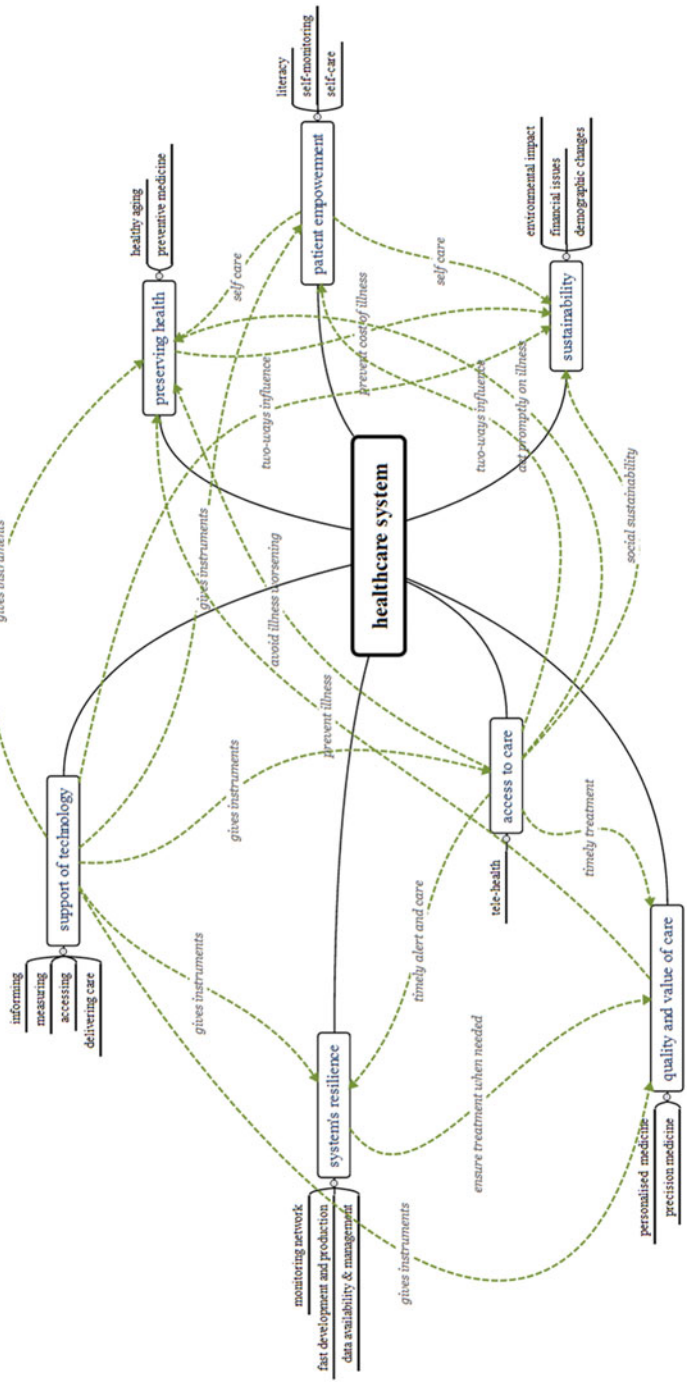

Fig. 14.1 The issues, targets and opportunities in the healthcare system and the contribution of medical device technology

services includes, among others, the logistics and availability of components and equipment, as well as the possibility to ensure the dedicated and timely contact between patients and caregivers. Obviously, these gaps are even more evident in healthcare systems of low-income countries or in countries without national health insurance programs.

Failure in providing the right quality of care, the lack of coordination in care delivery, an overtreatment or a treatment with low-value have been quoted among the main causes for the waste of resources in the US healthcare system [4, 5]. These considerations may also hold true for many other countries, primarily in the affluent part of the world.

These drawbacks can be overcome by the improvement of the Care Delivery Value Chain (CDVC) [6] by implementing a systemic application of medical devices and in particular innovative technologies. As illustrated in Fig. 14.1, this improvement is based on instruments and tools which allow to assist the ancillary HC activities. Among them are measures allowing to define, inform, assess and facilitate the access to care as well as supporting the delivery of the care itself.

14.1 The Questions

Even if we may not be as optimistic as Albert Einstein, and notably not able to solve complicated issues in less than 5 min. as being cited above, asking questions is always a good practice when dealing with complex topics.

The questions we have asked in the introduction of this book entitle us to elucidate possible ways to navigate the complex scenario as illustrated in Fig. 14.1 in more detail. Each co-author of this book was engaged to answer these questions on the basis of her/his experience and point of view and provide both a take home message and an outlook for future activities.

None of these questions has a simple and/or single answer. Each topic requires multiple perspectives and a suitable *helicopter view*. For this reason, each chapter underlines several different aspects, the most important are highlighted in the last column of Table 14.1.

14.2 The Role of Technology

Technology is one of the main and most pervasive topics in the map shown in Fig. 14.1. Taken together, aspects outlined here will result in a deep change in healthcare. Additional opportunities, like IoMT (Internet of Medical Things), AI (Artificial Intelligence), further advances in robotics, imaging and telemedicine, telehealth, precision medicine and extensive use of digital therapeutics (DTx) are going to come true [7, 8]. These solutions are expected to become standards in the next decades. Such advances will also have a deep impact on the outcome of sick

Table 14.1 The questions to be answered in this book

Questions	Answers in chapter(s)...	Key topics
What is the meaning of **value** in healthcare?	Chapters 1, 2, 8, 9, 10, 11	Value for the stakeholders, system resilience, access to care, cost and performance
How can the healthcare system and organisations pursue the **value, quality** and **sustainability of healthcare (HC)**?	Chapters 1, 2, 6, 8, 9, 10, 11	Generation of value, HC process management and technology support, performance of therapy and devices, risk management, reimbursement issues, environmental impacts, social sustainability
How to decide about the best applicable **medical technology**?	Chapters 2, 3, 4, 5, 6, 7, 8, 9, 10, 13	Appropriate testing and selection of devices, biocompatibility considerations, introduction of innovation, healthcare provider organisation
How to control the **quality and safety** of the application of medical technology?	Chapters 1, 2, 4, 5, 6, 7, 11, 13	Adequate testing, standards and regulations, risk management, application environment, devices development, patient's data security
How can a Healthcare Provider Organisation (HPO) optimise its **performance** with the use of medical devices and equipment?	Chapters 2, 6, 9, 10, 11	Qualified employees, device selection, application environment, risk management, process management, cost control and reimbursement schemes
What is the role of **innovation** in healthcare (medical devices)?	Chapters 2, 3, 4, 5, 13	Management of innovation, control of the achieved quality, defined target groups, personalised medicine, telehealth and ethics

patients given that additional financial resources are supplied. Promises and information about announced innovations by the involved industries and other stakeholders to the public and to patients have to be met. The often-heard notion "Too good to be true!" has a special meaning in healthcare and promises not kept may destroy the confidence into capabilities of medical devices to their disadvantage.

Remembering J.A. Schumpeter [9], innovation is the market introduction of new products and practices derived from the combination of existing products and technologies in different ways. This notion provides a basis for the exponential growth of technologies in different fields and in the medical field in particular. Examples are e.g. the combination of ICT, internet, and sensors for the online monitoring of vital parameters on the way to achieve a better patient's self-monitoring and a really effective telemedicine.

Here, with the term "technology" we refer to both the items strictly defined as "medical device", but also to any additional product, either hardware or software, that works on patients, possibly in connection with other items for diagnostic or therapeutic purposes. Among them are "Combination products", where medical devices are combined with biological cells or systems. They are experimentally used, e.g. in bioartificial livers or in bioartificial kidneys or in bioreactors [10, 11]. They show promising results when applied both in medical application and in *in vitro* diagnostics, such as a lab-on-a chip (LOC). LOCs are devices that integrate one or several laboratory functions on a single integrated circuit of the order of mm^2 or a few cm^2 to achieve automation and high-throughput screening [12]. Most recent innovations—with more than 3000 publications since 2009—refer to organoids in 3D configurations [13]. However, their clinical use and marketing requires complex approval procedures. These devices are qualified as medicinal drugs and not as medical devices according to their higher-ranking pharmaceutical "principal mode of action" under the EU ATMP-regulation (ATMP-Advanced Therapeutical Medicinal Products [14]). As a consequence, such combination products have to undergo timely Phase I-III clinical trials for approval and sales. The future of such devices will depend on financial resources, the interest of dedicated scientists and public acceptance.

It must again be noted that medical devices and combination products must comply with the regulations applicable to their "principal mode of action". Medical devices base on physically controlled modes of action and thus exhibit a certain level of risk when applied [14, 15], whereas combination products act preferentially by pharmaceutical means. The management of associated risks should be connected with both types of application. Ensuring Reliability, Reproducibility and (Re)-traceability (3Rs) of medical devices (as a major request in the MDR) and ATMPs is vital for the safety of patients and for caregivers either.

Recently developed technologies allow for the implementation of wearable sensors to assess vital parameters online, both invasively and noninvasively as a point-of-care device (POC). Applications have been reported to be useful in case of multiple sclerosis, allowing for the remote assessment of the progress of illness or the effectiveness of the therapy [16]. A landmark change in diabetes care came with the development of "continuous glucose monitoring (CGM)" via an indwelling subcutaneous sensor that could check interstitial fluid glucose readings every 3–5 min. CGM provides more frequent information on blood glucose and less invasively, than with the use of a traditional measuring instrument [17]. Under development is currently also a wearable microneedle, multifluidic insulin-sensing device which allows for closed-loop insulin-delivery systems. When available, direct and online tests of insulin levels might help increase the "time in range" for people with type 1 and type 2 diabetes [18].

An additional and important area of improvement is related to the "patient's journey".[2] In many situations a deeper involvement of technology (e.g. IT and remote monitoring) could make it easier and more effective in terms of cost and outcomes [19]. The assessment of physiological parameters and quality indicators with biosensors as a point-of care (POC) device is also useful to overcome the more and more important issue of the growing incidence of chronic diseases. In this context, a "bench-to-bedside" approach is also underway using neuro-prostheses, e.g. for the control and maintenance of blood pressure [20]. Implantable sensors, pacemakers, subcutaneously implanted devices, as well as left ventricular assist devices (LVADs) or even a total artificial heart (TAH) need electric batteries for their function. Current concepts follow the concept of miniaturising these batteries and improving their shelf life, such that they can be implanted in the body and to avoid infection by transcutaneous cables [21].

In fact, there is (always) an informative asymmetry between the doctor's visit and the daily life of the patient. What can be seen by the physician during the limited time of her/his visit may not fully represent the patient's experiences during her/his daily life. IoT application are one possible solution, another may be facial recognition of patients [22]. With the help of this technology, developed for the control of people in public areas, physicians might be able to profit in their diagnoses on patient's well-being in the future.

Of course, all the above requires the implementation of a powerful and reliable communication network, but also a more systemic approach, involving the storage of data, the possibility to share information based on data among the different platforms and individuals, such as caregivers, possibly via the FHIR (Fast Healthcare Interoperability Resources) standard. Last, but not least, it is required to dedicate attention and resources to the adequate training of all the involved stakeholders, including patients, lay and professional caregivers. The security of the involved IT system and the anonymous recording of data is also a mandatory issue.

14.3 System Approach

Medical device technology has made progress in recent years. Innovative ideas and concepts have led to considerable and positive improvements in global healthcare, of which we could mention only a few. Diseases can be earlier diagnosed and treatments initiated such that in many cases a win-win situation for patients, caregivers and health insurance funds can be observed. One reason for success is "System and

[2] A formal term for the sequence of care events which a patient follows from the point of entry into the system triggered by illness until the patient is discharged from hospital to his or her home, care home, hospice or due to death. [patient journey. (n.d.) Segen's Medical Dictionary. (2011). Retrieved June 22, 2021, from https://medical-dictionary.thefreedictionary.com/patient+journey].

design thinking". By these complex systems, such as the healthcare system can be successfully managed and possible negative emerging side effects and behaviours be counteracted in time [19].

The sentence by Dr. Irene Agyepong, indicated at the beginning of this chapter (quoted in [19]), is precious, since it underlines the need to apply the right systemic approach when dealing with the organisation of healthcare systems. This is absolutely important when considering both the prominent impact of innovation in healthcare and the number of different stakeholders. The systemic attitude is of particular importance when setting healthcare services in low-resources settings. The *leapfrog effect* can help to avoid the mistakes observed in the past by the now "more advanced" organisations.

The map in Fig. 14.1, besides providing a picture of the most relevant topics in actual healthcare systems, also suggests that an innovative approach has the potential to help for the solution of both technological and medical problems. This complex mix of opportunities and threats must be managed with a systemic and holistic approach to fully exploit the opportunities offered by medical device technologies.

Take Home Message

- The objectives of healthcare systems are to provide easy and timely access to therapies, guarantee the delivery of quality and value of care ensuring sustainability.
- Important factors are also the healthcare system resilience and the patient's empowerment.
- Medical devices and related innovative technologies, including "common" devices like a smartphone or upcoming face recognition system, may provide a strong support to reach these objectives.
- In all mentioned applications, it is mandatory to ensure that device's efficacy, safety and risks are adequately managed.
- The number of interconnected objectives, some of them performing even in a mutual potential conflict, and the number of involved stakeholders, are representative of a very complex scenario that needs to be addressed with both *a helicopter view* and a system approach.
- Following a system approach, technology and innovation are key elements to support improvement and sustainability of healthcare systems.

References

1. Kissik W (1994) Medicine's dilemmas infinite needs versus finite resources. Yale University Press
2. World Health Organization (2019) WHO guideline: recommendations on digital interventions for health system strengthening. ISBN 978-92-4-155050-5
3. Tanahashi T (1978) Health service coverage and its evaluation. Bull World Health Organ 56(2):295–303

4. William H, Shrank WH, Rogstad TL, Parekh N (2019) Waste in the US Healthcare system estimated costs and potential for savings. JAMA 322:1501–1509
5. Berwick DM (2019) Elusive waste—the Fermi Paradox in US health care. JAMA 322:1458–1459
6. Porter ME, Teisberg EO (2006) Redefining health care. Harvard Business School Publishing, Boston
7. Webster A (2007) Health, technology and society. Palgrave Macmillan, Basingstoke
8. Lehoux P (2006) The problem of health technology. Routledge Taylor & Francis Group, LLC, New York
9. Schumpeter JA (2010) (1947) Capitalism, socialism and democracy. Kessinger Publishing
10. Song J, Guyette J, Gilpin S, Gonzalez G, Vacanti J, Ott H (2013) Regeneration and experimental orthotopic transplantation of a bioengineered kidney. Nat Med 19:646–651
11. Kumar A, Tripathi A, Jain S, Tech M (2011) Extracorporeal bioartificial liver for treating acute liver diseases. J Extra Corpor Technol 43:195–206
12. Volpatti L, Yetisen A (2014) Commercialisation of microfluidic devices. Trends Biotechnol 32: 347–350
13. Lancaster M, Huch M (2019) Disease modelling in human organoids. Dis Model Mech 12. https://doi.org/10.1242/dmm.039347
14. European Parliament and Council (2007) Regulation (EC) No 1394/2007 of the European parliament and of the council of 13 November 2007 on Advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, Official J European Union, L 324/121
15. Nathan G, Cortez JD, Glenn I, Cohen JD, Kesselheim AS (2014) FDA regulation of mobile health technologies. N Engl J Med 371:4
16. Bianco D, Spreafico A (2020) White Paper "Sclerosi multipla e le tecnologie digitali: una proposta di patient journey digitally enhanced". Dicembre 2020. Milano: The European House – Ambrosetti
17. Maran A, Crepaldi C, Tiengo A, Grassi G, Vitali E, Pagano G, Bistoni S, Calabrese G, Santeusanio F, Leonetti F et al (2002) Continuous subcutaneous glucose monitoring in diabetic patients: a multicentre analysis. Diabetes Care 25:347–352
18. Rollet J (2020) Novel insulin sensor under development for point-of-care testing, insulin-delivery devices. Healio
19. De Savigny D, Adam T (eds) (2009) Systems thinking for health systems strengthening. World Health Organization, Geneva
20. Guyenet P (2021) Neuroprosthetic device to maintain blood pressure. Nature 590:223–224
21. Zhu M, Schmidt O (2021) Tiny robots and sensors need tiny batteries—here's how to do it. Nature 589:195–197
22. The Economist (2021) Image database on facial recognition programs. June 5, p 81