EXECUTIVE SUMMARY

Scope

The development, evaluation and introduction of medical innovations and technologies in general and innovative medical devices in particular are considered an increasingly important factor in addressing the grand societal challenge related to health and wellbeing. In view of the rapid technological advances in and the rising cost of health care, society expects new medical devices to have added benefits.

The main topic of this report is how to address the added benefits of medical devices. The overarching principle that actually drives the evaluation and regulation of any health care intervention, including medical devices, is:

To generate and accumulate evidence that the use of a device is not only safe but also has benefits, preferably added benefits beyond existing care, for the health or health care of the intended individuals, patients, professionals or for society at large.

Benefits can include a direct therapeutic effect yielding improved health outcomes for the targeted individuals or users. But it may also include indirect benefits by improving ease of use, facilitating or improving screening or diagnosis of diseases, or reducing the burden on patients or the costs associated with medical care. Establishing the benefits of medical devices poses specific challenges. This report provides tools to support and enhance the clinical research tradition of assessing those benefits.

Aim and targeted readership

The first aim of the report is to provide explicit guidance concerning the application of research methods and approaches suitable for assessing the benefits and performance of medical devices. The second aim is to tailor this guidance to the various device types and specifics, as well as to the contexts and indications in which they are used, and the individuals in and users by whom they are used.
This guidance is meant for all stakeholders involved in the evaluation, use, and regulation of medical devices, including researchers and professionals in health care, the medical device industry (SMEs in particular), Notified Bodies, health insurance companies, hospital boards, regulatory agencies, funding agencies and medical ethical review committees.

Motivation

In this report, the Royal Netherlands Academy of Arts and Sciences (KNAW) aims to contribute to the European Union’s request that its Member States ‘take into account that improved research frameworks and criteria are needed to enhance reliability, predictability, speed and transparency in the decision-making on the introduction, use and reimbursement of medical devices’. The specifics of medical devices, however, call for a tailored approach, as they could hamper innovation and economic opportunities in Europe.

Medical Device Variety and Specifics

Chapter 2 of this report offers an overview of the variety of medical devices and associated regulatory aspects. There are many different medical devices (almost 500,000). They are intrinsically diverse in terms of use, users, sector and policy, making it a complex matter to design and conduct valid research into a device’s merits.

- **Device use** differs in its aims (e.g. for diagnostic, prognostic, screening, therapeutic, or supportive purposes), durability (e.g. disposable vs. implantable) and mode of action. The need to collect evidence about its (added) benefits is more pressing the higher the risk involved in using a device. However, there is no need to explicitly establish clinical benefits for all medical devices that are used in health care: there is no one-size-fits-all.

- Consumers, professional caregivers and health care policymakers may have differing **user perspectives**. Consumers need to be assured that the use of the device is safe and has a positive benefit/risk ratio. Policymakers want the introduction of new, often costly devices to be safe, beneficial and cost-effective. Health care professionals share the concerns of both consumers and policymakers; they can, moreover, influence a device’s performance, benefits and safety by the way they handle it and by their skills.

- **The market** for medical devices stretches far beyond the professional care setting. Devices are sold by large European multinationals, by SMEs and over the counter. Decentralised health care solutions and widespread use of mobile technologies are opening up innovative ways of increasing patient self-management. The life cycle of medical devices is relatively short (2.5-6 years on average) and in many cases, incremental modifications improve a device over time.
All this contributes to the complexity of research assessing the benefits of device use.

**Stakeholders Views**

**Chapter 3** presents the results of a field survey among stakeholders. All of the stakeholders warned against comparing medical devices with pharmaceuticals and implementing a research paradigm similar to that used in drug approval and reimbursement. However, they also identified critical issues and challenges related to new developments and device evaluation:

- In recently amended EU legislation on medical devices, the emphasis on clinical evaluation has increased but actual guidance on how to design such research is not elaborated. More awareness is needed of the challenge posed by new types of medical devices, such as combination products and self-management products.
- Research into the benefit of a device *after* CE certification to encourage its use and uptake by intended users, suffers from inadequate knowledge of the pros and cons of different research approaches. Frequently, line extensions of existing devices have resulted in numerous small datasets, whereas research commonly takes place in highly controlled settings of experts having undergone extensive user training, which all is very different from regular care.
- There are safety issues related to device use in regular care because devices are commonly applied by untrained professionals. This report does not explicitly provide recommendations for training professionals in new device use, as this subject is addressed by the Dutch Order of Medical Specialists (OMS).
- Registries, including clinical data on using a device in regular care, are crucial for assessing the long-term safety, performance, benefits and cost-effectiveness of devices.
- Health technology assessments (HTA) are hardly ever conducted for medical devices, let alone endorsed. However, in the current era of evidence-based medicine, the benefits and economic considerations of device use need to be taken into account. This should ideally happen in an early phase of new device development.

**Research Approaches Tailored to Medical Devices**

Given the concerns of the stakeholders, **Chapter 4** focuses on the main principles of research into the performance, benefits and added benefits of medical devices. The chapter provides explicit guidance concerning the pros and cons of different study approaches, given the device specifics and the targeted context, patients and users of a device. This guidance enhances ones understanding of the available evidence, helps in planning subsequent studies, and improves the dissemination, uptake and application of *safe and beneficial devices* by professionals, patients and other stakeholders.
No one-size-fits-all approach

The guidance in Chapter 4 departs from the above overarching principle. It continues to make a distinction between two main categories of devices, therapeutic devices versus non-therapeutic devices. The latter include diagnostic, monitoring, screening or prognostic devices or rather tests. Therapeutic devices usually interfere directly with – often targeted – bodily systems and mechanisms. Examples are pacemakers, nerve stimulators, prostheses, breast implants and surgery robots. Therapeutic devices treat specific diseases directly, alleviate specific symptoms or complaints, or improve daily activities. Diagnostic, prognostic, monitoring or screening test devices do not treat or alleviate diseases, symptoms or signs directly, but indirectly. Examples include imaging tests, companion diagnostics, laboratory tests, or point-of-care tests. Such devices provide information to users, e.g. professionals or patients, which in turn direct subsequent actions (e.g. therapies or lifestyle changes) that may lead to benefits, e.g. improved health. However, test devices may also be beneficial because they facilitate better therapeutic action by medical drugs (such as companion diagnostics), or because they lead to less invasive, burdensome or costly detection of disorders (such as screening or point-of-care tests). Finally, unlike therapeutic devices, many test devices, e.g. imaging tests, are not intended for just one specific medical condition or indication.

Research approaches to assessing the risks, benefits and performance of both types of devices are markedly different. This is why there is no one-size-fits-all approach possible for the evaluation of medical devices.

Pathway of device benefits

The variation in devices is reflected in the many different working pathways or mechanisms through which each device leads to intended (benefits) and unintended (risks) effects on health or health care. Deciding which evidence and research are actually needed can first and foremost be enhanced by device developers, manufacturers and end-users (i.e. targeted professionals and patients) collaborating and describing in detail the potential pathways through which device benefits and risks are likely to arise. This working pathway is ideally defined in the very earliest development stages or even at the conception of a device. A detailed description of the following issues can serve to put evidence from different types of device studies – e.g. technical, safety and clinical studies – into a linked or network of evidence perspective:

- the anticipated technical or analytical capabilities of a device;
- the expected unintended and intended effects in the targeted context;
- in whom these effects are likely to occur, e.g. in the targeted individuals/patients, in the care providers or in health care at large;
- the anticipated mechanisms through which these potential risks and benefits will occur or be achieved in the intended context;
• the existing care in the targeted context and individuals;
• the expected time frame in which potential risks and benefits might occur.

The optimal study approach and alternative strategies

To accumulate evidence that the use of a device is safe and has positive effects on health or health care beyond those achieved by current practice, one could design an ideal study that measures all these aspects directly in the most valid and informative way. Chapter 4.4 describes the essentials of such a pragmatic or comparative effectiveness trial. Such randomised comparative effectiveness studies are methodologically much more challenging for medical devices than for medical drugs. This is due to the interplay between technical device complexities, user skills and learning-curve issues, all of which influence the benefits and risks of a device and its use. Alternative research approaches are needed to evaluate the performance and benefits of device use.

Three main approaches

To generate evidence that the use of a device has benefits, preferably added benefits beyond existing care, for the intended individuals, professionals or society at large, we can make use of three main study approaches, each with its own merits and vulnerabilities. Chapter 4.7 provides detailed guidance on these approaches, complemented by numerous examples applied to a variety of medical devices in Appendix IV.

1. Studies providing direct evidence of the benefits or added benefits of a device use for health or health care.
   Such studies basically address all the issues related to the device use as in practice, the intended context, a comparison strategy, the relevant effects and timing of these effects, and required study size. In addition to the ideal large-scale, long-term, comparative effectiveness trial, there are numerous alternative study approaches that may also provide direct evidence. These include the traditional randomised designs. But they also include more innovative and efficient randomised approaches, as well as non-randomised study approaches that can help generate direct evidence about the long-term performance and benefits of device use.

2. Studies providing indirect evidence of the benefits or added benefits of device use for health or health care, using a quantitative linked-evidence approach.
   Indirect evidence approaches have in common that they do not directly measure the ultimate health outcomes relevant for the targeted individuals, context or users. Instead, such approaches focus on outcomes measuring intermediate changes along the working pathway of device use. Indirect evidence approaches are very useful in situations where the direct evaluation of device use is absent. Their validity depends
on how well the ‘intermediate’ outcomes relate to long-term health (or health care) outcomes. Linked-evidence modelling approaches link various types of evidence, ranging from technical performance to clinical performance or clinical benefits studies. Quantitative linked-evidence approaches are very relevant for test devices and for devices that are modifications of an existing device. They can quantify to what extent a minor device improvement leads to health benefits for the targeted individuals, context and users, using study results from previous versions of the device.

3. Studies providing indirect evidence on the benefits or added benefits of device use on health or health care, using a qualitative linked-evidence approach. Evidence of a device’s benefits on long-term health or health care outcomes in a specific indication, context or user group, may also be inferred indirectly, for example, when adapting evidence from studies conducted in different individuals, patients or users or from studies across different indications of device use. Evidence gained from technical performance studies, safety studies, studies on related devices or preceding versions of the device, should be linked and put into perspective. This again requires knowing the working pathway through which device use may lead to benefits for health or health care. Inferences about the relevant, long-term health or health care benefits (and risks) of device use taken from such qualitative linked-evidence approaches do not have the same validity as the approaches discussed under 1 and 2. Nevertheless, qualitative linked evidence is currently often considered sufficient for market access, and perhaps even for reimbursement decisions.

Complementary issues

Chapter 5 addresses a number of issues that go beyond the explicit guidance for research strategies in Chapter 4, set against the backdrop of European policymaking concerning medical devices. These issues include: registries on the use of medical devices after market access; user involvement; end-user training; and evaluation of the cost-effectiveness (HTA) of devices.

Recommendations for stakeholders

- For researchers and industry, explicit guidance for assessing the benefits of device use is presented in Chapter 4 and illustrated across a wide range of medical devices in Appendices IV and V. If this guidance is properly introduced at an early stage of device development, a wealth of suitable research approaches becomes available.
- For regulatory agencies, including Notified Bodies, Competent Authorities, medical ethical review committees, and health research funders, Chapters 2 and 3 and Appendix III discuss general regulatory issues. These agencies will also benefit from the general research guidance described in Chapter 4 when judging device research proposals and interpreting the results of such research.
• For health care professionals and hospital boards, the guidance presented in Chapter 4 is useful for judging what evidence is actually available and what evidence is still lacking when deciding to purchase and implement a particular device.

• For health insurance companies and health care policy at large, Chapters 3 and 5 and Appendices III and VI demonstrate that medical devices have their own intrinsic issues and challenges. At the same time, Chapter 4 illustrates the level of evidence that the various research approaches should produce when judging the potential benefits of a particular device.

In conclusion

This report guides stakeholders involved in the evaluation, use, and regulation of medical devices, towards choosing the proper approach for assessing the benefits and performance of a device for health care, given the specifics of the device. The report also offers guidance on how to interpret existing evidence on the risks (safety), performance, and benefits of device use, and how to put this evidence into perspective so as to make better-informed decisions regarding the introduction, use, and reimbursement of a device. This guidance ultimately aims to protect society, users and end-users against the introduction and use of devices that are ‘unsafe’ or ‘unnecessary’.