Report 65/07 BMT/RB/RG/cvr

New and Emerging Medical Technologies
A horizon scan of opportunities and risks

RE Geertsma, ACP de Bruijn, ESM Hilbers-Modderman,
ML Hollestelle, G Bakker, B Roszek

2 February 2007

Contact:
RE Geertsma
Centre for Biological Medicines and Medical Technology
National Institute for Public Health and the Environment (RIVM)
Robert.Geertsma@rivm.nl

Abstract

New and emerging medical technologies will offer patients improved and personalised treatments, better prognosis and reduced recovery times. Consequently, new risks will also emerge. Issues related to risk management and regulation including requirements for training and education should be discussed with all stakeholders at a European level. Advances in imaging technology, biosensors and lab-on-a-chip devices will enable more precise diagnosis, at an earlier disease stage and at the point of care. Minimally invasive surgery techniques combined with sophisticated implant systems, constructed from innovative materials and possibly using state-of-the-art software and telemetry, provide continuously improving therapy options. New generations of medical technology products are more and more resulting from so-called "converging technologies", i.e. the combination of different technologies which leads to the crossing of borders between traditional categories of medical products such as medical devices, pharmaceutical products or human tissues. Furthermore, the trend can be observed that a growing number of diseases and disorders can be treated with technological solutions instead of medicines. Next to product specific risks, general aspects like unknown properties of new material classes, the combination of different technologies and increasing computerisation should be managed. Further risk management is needed because clinicians are facing a technology gap and need specific training to work with new technologies. On the other hand, innovation should not be hampered unnecessarily and that the availability of innovative technologies to patients should be pursued.

Contents

1.   Introduction

1.1   Background

Technology is generally regarded as the utilization or application of science to benefit society. In medical technology, innovations are evolving at a rapid pace, driven not only by scientific, but also by economic interests and the high value that is generally attributed to public health. Although this context is not new, it has been recognized that the number of new and emerging technologies is currently expanding at an increased speed.

New and emerging technologies inherently mean new risks. Questions have arisen whether the current regulations for medical technologies are adequate to deal with these new risks. It is considered a challenge for all stakeholders to deal with the risks in such a way that patient safety is guaranteed. Governments recognise the important role of design in ensuring patient safety and are working with all stakeholders to find ways of providing constructive feedback to manufacturers on general issues of product design and manufacturing practices. Furthermore, it is being evaluated whether the risks call for any amendments of current regulations. On the other hand, all involved parties feel that innovation should not be hampered unnecessarily and that the availability of innovative technologies to patients should not be jeopardized. The European Commission has installed a "New and Emerging Technologies" (NET) working group consisting of all stakeholders in order to deal with these issues at a European level.

The Dutch Ministry of Health, Welfare and Sport has commissioned a report describing the categories of new and emerging medical technologies that should be included in the discussions with stakeholders on the management of risks related to innovation.

1.2   Aims

The first aim of this report is to provide insight in recent advances in medical technology, by presenting a horizon scan of new categories of products, which have recently emerged on the market or are currently being developed and expected to become available within the near future. The second aim is to discuss the related (new) risks in general terms, in order to provide a basis for parties evaluating the question whether such risks are adequately covered by the current European regulations.

1.3   Scope

This report provides an overview of new and emerging medical technologies. The term "new" includes innovative applications and modifications of existing technologies. Therefore, the term "new and emerging technologies" is used in this report. The scope is limited to products that fall under the European Medical Device Directives [1-3].

Medical technology provides instrumentation and methods designed for the purpose of prevention, diagnosis, treatment, monitoring or alleviation of diseases or disabilities. Given the plethora of innovative products entering the market at an increasing speed, it is impossible to provide a complete overview. Product categories were considered relevant if

innovations are taking place which have a (potentially) large effect on the way health care is delivered to patients in terms of performance or if substantially increased levels of risk are envisaged. Since there are no objective parameters to substantiate whether either of these criteria could be met, the authors used their professional expertise and network to decide on this. Descriptions of the product categories in Chapter 2 are meant to provide a general impression of developments. In addition, several product categories have been explored in more depth and will be described more extensively in Appendices A-F. Selection of these product categories took place on the basis of a subjective rating of relevancy with regard to the aims of the report in combination with existing knowledge of the authors. As a consequence of the fact that medical technology is such a broad field and the applied selection methodology, it is acknowledged that additional product categories may exist, which meet the relevancy criteria equally well. Furthermore, the description of developments within one product category is not claimed to be exhaustive.

1.4   Method

This report was based on literature searches, internet searches, electronic newsletters and proceedings of conferences. Literature was identified from several sources including electronic databases and cross-checking of reference lists. Electronic databases consulted for scientific literature were Scopus™ (Elsevier BV), Medline/PubMed (US National Library of Medicine). Internet searches were performed starting from the search engine Google (www.google.com). Product information was obtained using manufacturers' websites which were identified using Google (www.google.com).

1.5   References

[1] Medical Devices Directive 93/42/EEC, Council Directive of 14 June, 1993. Available from:
     http://eur-lex.europa.eu/LexUriServ/site/en/consleg/1993/L/01993L0042-20031120-en.pdf. Accessed December 11, 2006.

[2] Active Implantable Medical Devices Directive 90/385/EEC, Council Directive of 20 June, 1990. Available from:
     http://eur-lex.europa.eu/LexUriServ/site/en/consleg/1990/L/01990L0385-19930802-en.pdf. Accessed December 11, 2006.

[3] In Vitro Diagnostic Medical Devices Directive 98/79/EEC, Council Directive of 27 October, 1998. Available from:
     http://eur-lex.europa.eu/LexUriServ/site/en/consleg/1998/L/01998L0079-19981207-en.pdf. Accessed December 11, 2006.

2.   Overview of new & emerging medical technologies

2.1   Definition

The early years of the 21st century show an acceleration of the introduction of innovative medical technologies. These will increasingly impact the quality of health care that can be delivered to patients and the location in which that care can be delivered. This revolution in the capabilities of medical technologies has been attributed to the coincidental emergence of several areas of science and technology which, when combined, will act as protagonists and strengthen each other. The most important areas involved are the biological sciences, nanotechnology, cognitive sciences, information technology and materials science. The resulting products are referred to in terms like tissue engineered products, smart materials, computer-assisted surgery systems and artificial organs. None of these terms is entirely exclusive and in fact many new medical devices will combine these technologies. Furthermore, new generations of medical technology products are now being produced that increasingly cut across traditional demarcation boundaries such as medical devices, pharmaceutical products or human tissues. Combined with the development and perfection of minimally invasive surgical techniques, these new generations of devices offer patients improved treatments, better prognosis and greatly reduced recovery times. The trend to combine different technologies and the crossing of borders between traditional categories of medical products is commonly referred to with the term "converging technologies". This concept is illustrated in Figure 2.1.
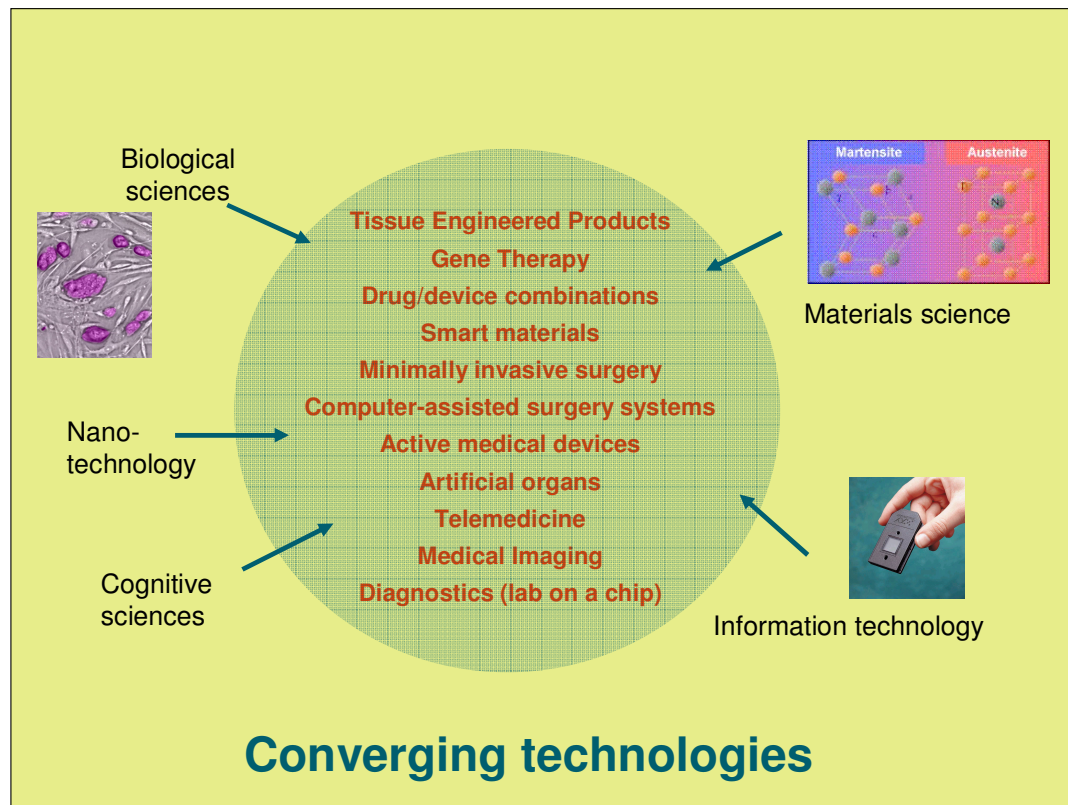

Figure 2.1: Illustration of the concept of converging technologies

Although it is acknowledged that new and emerging technologies are often combining different aims, this report is focusing on products with the primary intended use of a medical device. It has been recognized for a number of years that borderline products may be hard to classify either as a medical device or as a medicinal product. Therefore, the European Commission installed a Borderline/Classification Working Group and issued a guidance document on the demarcation between these two product classes [European Commission 2001]. While the European regulations on combination products utilizing live human or animal cells are still under development [European Commission 2005], similar guidance for such borderline products is not yet available. At a European level, the regulatory definition of medical device is currently also under discussion. Therefore, for this report, the definition as provided by the Global Harmonization Task Force is used [GHTF 2005], see Textbox 2.1.

Textbox 2.1: Definition of medical device [GHTF 2005]

`Medical device' means any instrument, apparatus, implement, machine, appliance, implant, *in vitro* reagent or calibrator, software, material or other similar or related article:

a) intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of:

- diagnosis, prevention, monitoring, treatment or alleviation of disease,
- diagnosis, monitoring, treatment, alleviation of or compensation for an injury,
- investigation, replacement, modification, or support of the anatomy or of a physiological process,
- supporting or sustaining life,
- control of conception,
- disinfection of medical devices,
- providing information for medical or diagnostic purposes by means of in vitro examination of specimens derived from the human body;

and

b) which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its intended function by such means.

Note 1: The definition of a device for *in vitro* examination includes, for example, reagents, calibrators, sample collection and storage devices, control materials, and related instruments or apparatus. The information provided by such an *in vitro* diagnostic device may be for diagnostic, monitoring or compatibility purposes. In some jurisdictions, some *in vitro* diagnostic devices, including reagents and the like, may be covered by separate regulations.

Note 2: Products which may be considered to be medical devices in some jurisdictions but for which there is not yet a harmonized approach, are:

- aids for disabled/handicapped people,
- devices for the treatment/diagnosis of diseases and injuries in animals,
- accessories for medical devices (see Note 3),
- disinfection substances,
- devices incorporating animal and human tissues which may meet the requirements of the above definition but are subject to different controls.

Note 3: Accessories intended specifically by manufacturers to be used together with a 'parent' medical device to enable that medical device to achieve its intended purpose should be subject to the same GHTF procedures as apply to the medical device itself. For example, an accessory will be classified as though it is a medical device in its own right. This may result in the accessory having a different classification than the 'parent' device.

Note 4: Components to medical devices are generally controlled through the manufacturer's quality management system and the conformity assessment procedures for the device. In some jurisdictions, components are included in the definition of a 'medical device'.

2.2   Overview

2.2.1   Nanotechnology

Nanotechnology is the design, characterisation, production and applications of structures, devices and systems by controlling shape and size at the nanometre scale, where properties differ significantly from those at larger scale. Nanotechnology cannot be considered a single product category. Instead, it is an enabling technology which is impacting most of the currently emerging medical technologies in some way. However, in view of the special position nanotechnology is taking these days with regard to research efforts, industrial investments, development of regulatory guidance documents, political statements and media attention, a separate paragraph is considered appropriate in this overview.

The potential impact of novel nanotechnology applications on disease diagnosis, therapy, and prevention is foreseen to change health care in a fundamental way. Furthermore, selection of therapy can increasingly be tailored to each patient's profile. In particular, relevant nanomedical applications are reported in surgery, cancer diagnosis and therapy, biodetection of disease markers, molecular imaging, implant technology, tissue engineering, and devices for drug, protein, gene and radionuclide delivery. Many nanomedical applications are in their infancy. Still, an increasing number of products are currently under clinical investigation and some products are already commercially available, such as surgical blades and suture needles, contrast-enhancing agents for magnetic resonance imaging, bone replacement materials, wound dressings, anti-microbial textiles, chips for *in vitro* molecular diagnostics, microcantilevers, and microneedles [Roszek et al 2005].

While product development is progressing rapidly, sufficient knowledge on the associated toxicological risks is still lacking [Jong et al 2005]. Reducing the size of structures to nanolevel results in distinctly different properties. As well as the chemical composition, which largely dictates the intrinsic toxic properties, very small size appears to be a predominant indicator for toxic effects of particles. For medical applications, immobilized nanostructures inside or on surfaces of medical devices such as surgical implants are expected to pose a minimal risk as long as they remain fixed. For medical applications utilising free nanoparticles or nanostructures, for example novel drug delivery systems, the specific toxicological properties have to be investigated. It is insufficient to rely on knowledge of the classical toxicity testing of chemical(s) and materials when the risks of nanoparticles and/or nanostructures have to be assessed.

2.2.2   Tissue engineered products

Another often cited emerging technology is tissue engineering, where combinations of materials, biomolecules and human cells lead to products with great potential in regenerative medicine. Tissue engineering has been defined as the application of principles and methods of engineering and life sciences towards fundamental understanding of structure-function relationships in normal and pathological mammalian tissues and the development of biological substitutes to restore, maintain or improve tissue function [Skalak 1988]. The products that arise from these techniques may provide an alternative to available therapies to replace damaged, injured or missing body tissues. Not only tissues like skin, cartilage or bone can be grown artificially, but research is also directed towards the development of artificial organs like heart, kidney or liver (see also Section 2.2.10). An important trend is the increasing use of stem cells, which are versatile, vital cells that can be stimulated in practically any desired tissue type.

Risks related to the use of products incorporating live cells have been recognized for a number of years now (see for example RIVM reports on risk management, biological safety evaluation and disease transmission related to tissue products [Wassenaar et al 2001, Tienhoven et al 2001, Tienhoven et al 2002]). Furthermore, regulators from both medical devices and medicinal product areas have studied this product category and have sought ways to deal with the regulatory gap they have created. The past few years, European regulations have been under development specifically to deal with all so-called advanced cell therapy products, including tissue engineered products, cell therapy products and gene therapy products [European Commission 2005]. It is currently not clear whether any products containing live cells will fall under the medical device directives. Therefore, these products are not elaborated on in this overview.

2.2.3   Drug device combinations

The product category where a medicinal product and a medical device are combined into one product is growing, and presents increasing problems of classification. Great innovations have been made possible in drug delivery, especially by the application of nanotechnologies (see also Section 2.2.1). For these products, the device-like component is only the carrier for the drug, so the combination product is a medicinal product, which falls outside the scope of this report.

Some of the older examples where modifications are still occurring include bone cements with added antibiotics and bone filler materials with biomolecules such as growth factors embedded in their matrix. Also hip implants with porous coatings carrying antibiotics or growth factors stimulating bone ingrowth have been known for some time now. This is, however, still an area where innovations are taking place, especially with the increasing control over the development of nanoporous structures which appear to be very suitable to carry drug components with a beneficial ancillary function. More recently, coated hip implants have been seeded in a clinical laboratory with cells taken from the patient, and implanted only after growing a sufficient number of bone cells inside the coating. These products are also considered during the ongoing regulatory discussions referred to in Section 2.2.2. Drug-eluting stents are currently the drug device combination products where most innovations are taking place. Developments in this product category are discussed in Section 2.2.4.

New risks that can be attributed to combination products in addition to the risks of the individual components are mostly related to interaction and compatibility. Material properties may be influenced by interaction with the drug component and a drug could for example be chemically changed, or its release profile might change when a different material is used or when material properties change after implantation of the combination product. In each of these cases, adverse toxicological or immunological reactions may occur or the intended purpose of the product or one of its components, for example an antimicrobial effect of a drug, may not be achieved.

2.2.4   Drug-eluting stents

In 2000 the first-in-man study commenced using immunosuppressive sirolimus-eluting stents implanted in coronary arteries [Sousa et al 2001], followed quickly by antiproliferative paclitaxel-eluting stents [Grube et al 2003]. Nowadays, drug-eluting stents have become the most widely used modality for coronary revascularisation interventions. The first-generation drug-eluting stents were manufactured using stainless steel and contained medicinal substances controlling neointimal proliferation by inhibiting smooth muscle cell proliferation, and/or having anti-inflammatory properties. Next-generation versions have focused primarily

on easier deliverability and are already CE-marked. In addition, several companies have tried to emulate or improve on the success of first-generation drug-eluting stents by developing new immunosuppressive drugs, such as biolimus, everolimus, and zotarolimus. Likewise, innovation in stent composition and design continues, with many second-generation drug-eluting stents replacing stainless steel with alloys (e.g., cobalt-chromium) that maintain radiopacity and strength but permit thinner, more flexible struts.

Perhaps the biggest and most controversial activities centre on the actual mechanics of drug-delivery and the need for a polymer coating. Polymers have been hailed by some as essential to controlled drug elution and maligned by others as a ticking time bomb: the potential cause of increased late thrombosis and other adverse tissue responses. The polymer has been blamed for stent-delivery glitches; in particular, the increased friction or 'stickiness' between delivery balloon and stent itself. New stents are being developed with polymer coatings that will disappear over time (bioabsorbable) (e.g., Grube E et al 2004) or coatings only on the outer (abluminal) surface of the stent. The idea is to direct drugs at the vessel wall, and not the bloodstream. Researchers recommended drug-eluting stent coatings to be routinely tested for being tightly anchored into the stent surface because loose particles would cause potentially serious adverse effects.

Another innovation in drug-eluting stent development is the concept of tiny drug reservoirs or wells where the drug can be loaded, rather than plastered over the entire outer and inner surface area of the stent. These drug reservoirs can be designed for abluminal as well as for luminal elution, such that antiproliferative drugs could be released in one direction and antiplatelet drugs in another. The polymer coating can be used within the small wells embedded in the stent where the drug is loaded, leaving the actual surface of the stent polymer-free.

Second-generation stent manufacturers focusing on bioabsorbable polymers are for the most part basing their technologies on elements that are already well established in the coronary stent R&D: drugs delivered via metal stents. Beyond these are devices described as "third-generation" devices, namely fully bioabsorbable stents, made completely of dissolving metallic stents (e.g., magnesium alloys) [Heublein et al 2003, Bose et al 2006], or (co)polymers (e.g., poly-L-lactic acid and poly-L-glycolic acid) [Ormiston et al 2007] which offer the potential of increased drug loading. Such bioabsorbable stents provide initial scaffolding support that prevents vessel recoil and negative remodelling but without the continuous vessel trauma caused by a permanently implanted stent.

A new technology has been developed based on a tissue engineering concept to reduce in-stent restenosis and thrombosis. It represents a new treatment paradigm in contrast to the pharmacological approach that interferes with the lesion healing. The promotion of healing in the vascular endothelium may be a more natural and consequently safer approach to the prevention of restenosis. A recent innovation is represented by a bio-engineered stent that focuses on the recruitment of endothelial progenitor cells to establish a functional endothelial monolayer, thereby providing the endogenous modulators necessary for efficient healing following stent implantation. A confluent endothelium provides a barrier to circulating cytokines and produces powerful inhibitors of smooth muscle cell proliferation, migration, and matrix production, potentially decreasing the risks of neointimal proliferation and thrombus formation. This non-eluting stent, which is already CE-marked, constitutes of anti-CD34 antibodies immobilised on the stent surface [Aoki J et al 2005]. Endothelial progenitor cells, which originate from bone marrow and circulate in the bloodstream, are then captured by these antibodies, leading to the rapid formation of an endothelial layer over and between stent struts.

The application of nanotechnology to modify stent surfaces may create new opportunities to improve stent performance. Recent efforts are focussed on nanoporous coatings, such as

diamond-like carbon, carbon/carbon composite, semisynthetic carbohydrates, hydroxyapatite, silicon carbide, and ceramic aluminium oxide.

In addition to the above described stent developments, indications for drug-eluting stent implantations are broadened. Drug-eluting stents are being clinically investigated or have received clearance for indications such as diabetes, coronary arteries with long lesions or smaller vessel diameter, peripheral artery diseases, bifurcation lesions, and left main coronary artery disease.

Compared to bare metal stents, drug-eluting stents considerably reduce the incidence of in-stent restenosis (for a recent meta-analysis see e.g. Babapulle et al 2004). Recently, clinical follow-up has revealed significant concerns relating to the incidence of late (>30 days) stent thrombosis, especially in long stents and after discontinuation of dual antiplatelet therapy [Mereno R et al 2005]. A clinical alert issued by the Society for Cardiovascular Angiography and Interventions as part of the recommendations made by the FDA's Circulatory Systems Device Panel provides recommendation for use of dual antiplatelet therapy in drug-eluting stent recipients, and recapitulates the panel's conclusions for on-label and off-label use of drug-eluting stents [Hodgson et al 2007].

The Clinical Evaluation Task Force (CETF) of the European Commission is preparing guidance on how to conduct clinical investigations with stents and the European Medicines Evaluation Agency (EMEA) is developing specific guidance for the assessment of the drug component of these products [http://www.emea.europa.eu/pdfs/human/ewp/5647706en.pdf].

2.2.5   Smart materials

Smart materials respond to environmental stimuli by changing either their properties (mechanical, electrical, appearance), their structure or composition, or their functions. A well known example is formed by the shape and memory alloys. Nickel-titanium alloys exhibit two very unique properties, pseudo-elasticity, and the shape memory effect. This can be used for the development of e.g. bone plates, robotic fingers/artificial muscles or stents. Also sutures with pre-programmed knots have been developed, which could be advantageous in e.g. minimally invasive procedures. New, specific risks for such products could be related to the timing of the memory effect. This could result for example from device failure or environmental stimuli, or it could be related to use errors and/or insufficient training.

Another example is formed by fast acting hydrogels, which are pH or temperature sensitive materials useful e.g. for drug delivery. Nano-structured "smart" membranes/surfaces are likely to advance the development of programmable, or feedback-controlled, *in vivo* drug delivery devices. Combining a "smart" surface or membrane with an otherwise diffusion-controlled delivery device permits the release rate to be regulated by changing the permeability of the membrane. Switchable surfaces and membranes can be controlled by light, heat, pH, and redox and amperometric reactions. New risks are formed primarily by environmental stimuli inadvertently setting off the switch, leading to dosing problems.

The term "smart" textiles is derived from intelligent or smart materials. Smart textiles are context-aware textiles which are able to react and adapt to stimulus from the environment. Smart textiles can be divided in passive smart textiles, active smart textiles, and very smart textiles. Passive smart textiles can only sense the environment and they are sensors. Active smart textiles have a sensing function and they act also as actuators. Very smart textiles take a step further, allowing to adapt their behaviour to the circumstances.

Smart textiles play a key role in the development of biocommunicative clothes for ambulatory measurement and monitoring of vital physiological, kinematic, and behavioural human parameters. Integration of sensors, actuators, and communication systems into woven or knitted textiles is now feasible providing light and wearable user-friendly electronic

systems capable of exchanging information with other health-related information systems. Several products are already on the market. Foreseen applications in healthcare are medical monitoring in obstetrics, pharmaceutical trials, geriatric care, (post-surgery) rehabilitation, detection of sudden infant death syndrome, mental health and drug delivery. New risks are mainly related to failures of the communication systems, possibly leading to false diagnoses and subsequent inadequate treatment.

2.2.6   Minimally invasive surgery and robotics

The laparoscopic revolution in minimally invasive surgery opened a new chapter in surgical history that has been characterized by rapid changes as the underlying technology continues to evolve. New techniques are under development in most fields of surgery, all with the potential to gradually replace or enhance the standard 'open' procedures.

Before introducing MIS techniques in medical practice, each individual treatment must be evaluated relative to existing alternatives on the evidence of the patient's benefit, surgical morbidity, general and procedure specific risks, short- and long-term outcome including complication rates and cost effectiveness. Only if this is carried out in a responsible way, and if sufficient education and training is provided to the users, then MIS procedures can be applied safely and to the advantage of the patient. Patient safety cannot be compromised just for the sake of a smaller incision.

A number of the MIS techniques are (partly) relying on computer and/or robot assisted surgery systems, also referred to as robotics. This provides means to perform more complicated procedures by MIS techniques, and also certain routine procedures can be performed more quickly and easily. Again, although the advantages are apparent, caution should be exercised before applying robotics in all types of interventions where they could be used theoretically before safe and effective clinical use has been carefully investigated. Especially here, education and training of the users is a prerequisite.

A more extensive overview of developments in this area and related risks is provided in Appendix A of this report.

2.2.7   Closed loop feed-back systems

Closed-loop feedback systems are systems that use mathematical algorithms to convert measurement results into outputs like administering medication. An important emerging medical application of closed loop systems can be found in the field of diabetes treatment. Closed-loop systems may also be used in anaesthesia and in muscle and neural stimulation or relaxation (including pacemakers, intracardiac devices and devices for epilepsy prevention). It is essential that such systems react promptly and properly on a diversity of physiological conditions and events. Furthermore, closed loop systems taking over control means that it may take some time before medical professionals or patients detect a deviation in device functioning, or a device action that is deteriorating or fatal for the patients health. Therefore, failing of closed loop systems may have serious consequences for patients. This means that closed loop systems controlling critical physiological processes should have to meet very stringent requirements with regard to performance and reliability before they are placed on the market. Data transfer between the components must be impeccable. Risk assessment and clinical studies should be extensive and take into consideration all possible physiological conditions and environmental circumstances.

Because closed loop systems are complicated devices, some of which generate a considerable amount of data to be analyzed or dealt with, extensive training of medical professionals and/or patients is of essential importance.

A more extensive overview of developments in this area and related risks is provided in Appendix B of this report.

2.2.8　Active implantable medical devices for neuroprosthetics

Active implantable devices constitute a broad category. Due to the fact that the devices are implanted, combined with the use of an energy source, they carry an intrinsically high risk. Moreover, this type of devices is most often implanted in or connected to the most vital physiological systems of the human body, i.e. central/peripheral nervous system or heart. This paragraph is mainly focussing on central nervous system applications. An overview of developments in new generation active implants for cardiac applications is provided in Section 2.2.9.

Deep brain stimulation of subcortical structures was initially applied for the treatment of tremor related to Parkinson's disease and essential tremor [Benabid et al 1996]. Currently, deep brain stimulation is under clinical investigation for a variety of other neurological and psychiatric conditions, such as dystonia, epilepsy, traumatic brain injury, Tourette's syndrome, obsessive-compulsive disorder, pain, cluster headache, and depression. The mechanism of action of deep brain stimulation remains controversial, but it is likely to relate to activation of efferent axon fibres and resulting downstream physiological effects. Improvements in surgical techniques based on technological advances, such as the introduction of 3-Tesla magnetic resonance imaging into common clinical usage, may simplify and improve subcortical targeting. Stereotactic frames may also evolve into tailored mini-frames and platforms using frameless stereotactic localisation to identify targets. The introduction of rechargeable pulse generators may make units lighter and save patients the risk and inconvenience of further surgeries. Other improvements in hardware include rechargeable batteries and automated parameter adjusting algorithms. Another challenge to effective deep brain stimulation is postoperative management. After the system is implanted, a clinician sets the stimulation parameters. Software assists in determining which stimulation parameters may be optimal. Medtronic, Inc. (Minneapolis, MN, USA) is the leading manufacturer of deep brain stimulation systems.

Stroke is often characterised by incomplete recovery and chronic motor impairments. Rehabilitation of an impaired motor function may occur due to the recovery of brain areas with limited or temporary insult. Alternatively, restoration of function may be the consequence of a process known generically as 'reorganisation', in which areas of the brain take over the function of stroke-damaged areas. The latter mechanism falls under the concept known as neuroplasticity. The brain's cerebral cortex, with its extensive network of interconnected neurons, is a very likely site of neuroplasticity. Device-assisted cortical stimulation of the motor cortex in conjunction with rehabilitative training helps stroke patients suffering from motor deficits and aphasia [Brown et al 2003]. Stroke patients receiving this type of therapy regain partial use of the affected limb or regain speak or correct word processing. Cortical stimulation of healthy brain tissue adjacent to the stroke-affected site, in combination with rehabilitation, enhances motor recovery and suggests that cortical stimulation for stroke patients may facilitate neuroplasticity. A pulse generator sends a low current through a wire to an electrode placed surgically atop the dura mater. Surgeons pinpoint the site using 'neuronavigation' techniques, including functional magnetic resonance imaging removing a part of the skull to access the dura. Further optimisation of the cortical stimulation therapy is needed for improvement of post-stroke recovery of (language) motor function. Northstar Neuroscience, Inc. (Seatle, WA, USA) is currently developing an investigational device, the Northstar Stroke Recovery System.

Other developments in the field of neural rehabilitation engineering are brain computer interface or brain machine interface systems. These systems are communication systems that allow a subject to act on his environment solely by means of his thoughts, without using the brain's normal output pathways of peripheral nerves and muscles [Wolpaw et al 2002].The brain computer interface system reads out the intentions of the patient via a microelectrode array implanted in the primary motor cortex and translates them into physical commands which control actuators, e.g. muscles or devices. Patients with motor disabilities, such as amyotrophic lateral sclerosis or spinal cord injury patients can benefit from such a system by using specific brain activations to communicate via a computer [McFarland et al 2005] or to open and close a prosthetic hand and perform rudimentary actions with a multi-joint robotic arm [Hochberg et al 2006]. The BrainGate™ is an investigational device and has recently been implanted in two subjects with spinal cord injury and one with advanced amyothrophic lateral sclerosis. The next goal is to use recorded signals to restore partial arm and hand function to people with paralysis due to high cervical spinal cord injury. The development of this system is a collaborative effort between Cyberkinetics Neurotechnology Systems,- Inc. (Foxborough, MA, USA), Case Western Reserve University and the Cleveland Functional Electrical Stimulation Center (Cleveland, OH, USA).

2.2.9 Active implantable medical devices for cardiac applications
The most important two classes of active implants used to assist or replace the heart function are blood pumps and cardiac pacing and defibrillation devices.

Because of the limited availability of donor organs and the urgency of cardiac support, ventricular assist devices capable of (completely) supporting the circulation are taking an increasingly important role in heart failure therapy. These devices provide circulatory support for bridge to transplantation, bridge to recovery or long-term chronic support. The newest generation of devices includes axial flow and centrifugal pumps. Many devices include magnetically levitated rotating propellers (impellers).These devices are smaller than former generation and potential advantages include durability, simpler mechanics, quiet function, and lack of valves.

Currently, two devices are being developed as total artificial hearts. Tremendous engineering efforts have been put into the R&D of total artificial hearts. In the USA total artificial hearts are under clinical investigation and premarket approval is expected for 2008. In Europe total artificial hearts are being tested preclinically.

Haemorrhage, air embolism, progressive multi-system organ failure are the most common causes of early morbidity and mortality after placement of a blood pump. The most common complications in the late postoperative period are infection, thromboembolism, and failure of the devices.

New models of cardiac pacemakers and cardioverter-defibrillation devices enable stored diagnostic information. This information provides crucial data about device and lead function, and arrhythmias discovered with device interrogation and is invaluable when troubleshooting problems with devices. Better diagnostic data allow for earlier and more accurate identification of device malfunction as well as better arrhythmia management. Additionally, advances have been made in hardware, leads, and better algorithms.

A more extensive overview of developments in blood pumps, including (ventricular) assist devices and total artificial heart is provided in Appendix C of this report. A more extensive overview of developments in cardiac pacing and defibrillation devices and related risks is provided in Appendix D of this report.

2.2.10   Artificial organs

Artificial organs can be defined as products that are intended to be used for the (partly) support, replacement or regeneration of diseased, damaged or otherwise not functional organs. Emerging technologies enable the development of increasingly sophisticated products. One way of creating artificial organs is the use of cell therapy and/or tissue engineering techniques, which fall outside the scope of this report (see also Section 2.2.2). Also non-cellular solutions based on mechanical, optical, (electro)physical or other technological characteristics are being developed, however. Examples are some of the active implantable devices for cardiological applications described in Appendix C, which could be called artificial hearts and the closed loop systems for diabetes treatment described in Appendix B, which could be interpreted as an artificial pancreas. Also for other organs such as the liver, kidneys, lungs, bladder and the gastrointestinal tract important innovation is taking place. In 2007, RIVM will publish a report which elaborates on these developments.

2.2.11   Telemedicine

Telemedicine is the practice of medical care using interactive audio visual and data communications. This includes the delivery of medical care, diagnosis, consultation and treatment, as well as health education and the transfer of medical data.' A number of closely related concepts and terms such as telecare, telehealth, telemonitoring, telemetry and eHealth are also being used. In principle, telemedicine is not new. Telemedicine can be as simple as a telephone interview, possibly supported by a videolink, faxing or e-mailing X-rays, ECG's, or other investigation results, or sending samples to a consulting physician or medical laboratory. Of great importance for modern telemedicine or eHealth applications are the multiple innovations taking place in information and communications technologies, and especially the increasing possibilities for internet and wireless communication.
Probably the most important risk of telemedicine and telemetry is related to errors in data transmission, leading for example to false diagnoses and subsequent inadequate or falsely indicated treatment. Errors can be related to any kind of system failure, however, the largest recognised source of errors is electromagnetic interference with other wireless devices such as telephones, laptops, palmtops or other medical devices. Another common problem is signal fading, during which the signal is momentarily lost. This can result in inaccurate signals, false alarms and loss of monitoring data. Furthermore, patient privacy could be jeopardised if the protection of data has not been secured, for example when electronic patient records are used. The use of the Internet, as most specifically mentioned in the concept of eHealth, obviously adds to the concerns of data protection. Internet hackers have already proved that it is possible get access to such systems. Finally, an important hurdle in the application of telemedicine service can be the incompatibility of hardware and software systems. It can occur that equipment will only communicate correctly if all components come from the same manufacturer.
A more extensive overview of developments in this area and related risks is provided in Appendix E of this report.

2.2.12   Medical imaging

Medical imaging technologies provide several of the most powerful diagnostic tools available to modern medical science. The ever improving resolution allows very early disease diagnosis leading to much better prognosis. Moreover, the importance of imaging in monitoring the effectiveness of treatment is likely to increase and recent advances have allowed surgical procedures under real time imaging guidance to replace open surgery in several areas [Persson 2006]. Minimally invasive surgery techniques are progressing rapidly

at least in part because of the availability of imaging modalities and the immense possibilities offered by interventional radiology. Precise, minimally invasive therapeutic interventions delivering ultrafine surgical instruments, radiation and in future gene therapy exactly at the desired spot without damaging surrounding tissues would otherwise not be possible, see also Appendix A. Current clinical practice is thus becoming increasingly dependent on the information provided using imaging techniques.

Since the introduction of X-ray machines at the end of the 19th century, and the development of imaging devices using internally administered radionuclides in the middle of the 20th century, diagnostic imaging has been an important tool. Such important innovations are nowadays taking place, however, that they should be characterised as emerging technologies. Computed tomography (CT), single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging (MRI), optical imaging, and ultrasound have all evolved steadily the past decades. More recently, however, big steps have been taken by integrating different imaging modalities in one system. Combining pathophysiological imaging with high resolution anatomic data allows the result to be much more than the sum of the parts. Strauss [2006] describes some of the opportunities and concerns that this marriage of imaging techniques is presenting to future medical practice.

PET and SPECT are molecular imaging techniques. Molecular imaging is the science of visually representing, characterizing, and quantifying (sub)cellular biological processes in intact organisms. These processes include gene expression, protein-protein interaction, signal transduction, cellular metabolism, and both intracellular and intercellular trafficking. Molecular imaging has the potential to quantify these events in three dimensions, and to monitor these events serially in time. Thus, biological processes can be identified in space and time with high spatial and temporal resolution. The emergence of molecular imaging has coincided with and has been made possible by the enormous advances in molecular biology, cell biology, transgenic animals, as well as the development of imaging probes that are specific, reproducible, and quantifiable.

PET and SPECT thus provide high quality functional information. The main difficulty to overcome is the lack of an anatomical reference frame. Correlation with the high resolution morphological and anatomical information from CT combines the advantages of both techniques. The successes of PET/CT and SPECT/CT, especially in oncology and cardiology have been described well in literature [Townsend et al 2004, Lodge et al 2005, O'Connor and Kemp 2006, Horger and Bares 2006].

In cardiology, the non-invasive imaging techniques have vital importance because one wants to reduce the number of invasive catheter angiograms, which are undesirable if not to be combined with a therapeutic intervention. In the US, nowadays coronary artery disease is mostly assessed using non-invasive imaging technologies [Guthberlet 2006]. Hybrid systems realise complementary information of anatomy and physiology at the same imaging session, providing the cardiologist with an expanded set of data on the condition of the heart in a short time, possibly increasing the trend already set using primarily single SPECT.

In oncology, PET/CT and SPECT/CT exert their impact on (early) diagnosis, staging and therapy monitoring. The introduction of whole-body imaging modalities has again substantially expanded diagnostic options, especially with regard to screening in tertiary prevention, i.e. to detect tumour recurrence or metastatic disease in oncological patients [Schmidt et al 2006].

The disadvantage of PET, SPECT and particularly CT is that these techniques involve the use of ionising radiation, which implies health risks. An alternative technique is MRI, which apart from the lack of ionising radiation, also provides excellent tissue contrast and detailed morphological information, especially in soft tissues. MRI, another form of molecular imaging, has evolved as a major important diagnostic technique in clinical radiology. The

advent of high magnetic fields, improved gradient coils and pulse sequences has provided the means to obtain three-dimensional images of humans at near cellular resolution. Signal intensity in tissue is manipulated by administration of exogenous contrast agents, which sharpen the contrast by affecting the magnetic spin of protons in water molecules in their proximity. Traditional MRI contrast agents are classified into paramagnetic and superparamagnetic materials. Novel contrast agents can also be based on the use of engineered nanoparticles [Roszek et al 2005]. Metal ion toxicity is an unfortunate consequence of physiologic administration of contrast agents but can be mitigated somewhat by complexation of the metals with organic molecules. Furthermore, toxicity of nanoparticles needs to be addressed with special attention (see also Section 2.2.1) High magnetic fields allow a better spatial resolution and better signal-to-noise ratios. A concern might be related to the increasing attractive force on metallic implants, potentially causing movements and the possible heating effect on metals. Such aspects are under investigation with MRI systems of different field strengths up to 7 Tesla [Shellock 2001, Shellock and Forder 2005, Cunningham et al 2005, Schrom et al 2006, Thelen et al 2006].

MRI is used increasingly in several clinical disciplines including cardiology, neurology, gastro-enterology, psychiatrics and oncology [Guthberlet 2006, Schmidt 2006, Edwards van Muyen 2006]. For oncology, especially whole body MRI scans are seen as a very important tool.

Most recently, a fusion between PET and MRI has been realized, which improves diagnostic accuracy by compensating disadvantages and combining advantages of both technologies [Zaidi 2006, Wagenaar et al 2006, Cherry 2006]. Whole body PET/MRI has even been advocated as the future in oncological imaging [Seemann 2005].

Finally, with regards to all the above developments, Strauss [2006] has made an important observation. To interpret the images produced by the combined imaging modalities, additional training in both anatomy and radionuclide imaging is needed. He states that a new breed of nuclear medicine technologists and practitioners will have to be trained for this. Provisions for this should be made in the curricula of these medical specialists.

2.2.13   Diagnostics

Apart from the medical imaging methods described in the previous paragraph, there are a few other important developments with regard to diagnostics in the 21st century.

From the technical point of view, some of the greatest innovations in diagnostics have been enabled by the application of nanotechnology. An area with near-term potential is detecting molecules associated with diseases such as cancer, diabetes mellitus, neurodegenerative diseases, as well as detecting microorganisms and viruses associated with infections, such as pathogenic bacteria, fungi, and HIV viruses. Macroscale devices constructed from exquisitely sensitive nanoscale components, such as micro-/nanocantilevers, nanotubes, and nanowires, can detect even the rarest biomolecular signals at a very early stage of the disease. Development of these devices is in the proof-of-concept phase, but they may be entering the market sooner than expected [Roszek et al 2005].

Furthermore, medical devices for *in vitro* diagnostics, such as gene-, protein- or lab-on-a-chip devices often applying nanoarray or microarray technology, are being developed in rapid pace. Numerous devices and systems for sequencing single molecules of DNA are feasible. Nanopores are finding use in new technology for cancer detection enabling ultrarapid and real-time DNA sequencers. In general, developments in protein-chips and lab-on-a-chip devices are more challenging compared to gene-chips and these devices are anticipated to play an important role in medicine of the future [Roszek et al 2005].

The abovementioned advances in combination with improved data handling and related IT systems, improved liquid handling and processing system technology, and increasing advances in microfluidic technologies have now removed technological aspects as a barrier for large scale point-of-care (POC) diagnostics [Huckle 2006]. This means that a great number of medical decisions at the bedside in hospitals or at the general practitioner's office could be based on measurement results which are immediately available with the patient present. For example, apart from already established POC test systems for blood glucose monitoring and anticoagulant therapy, devices are being developed for the detection of several infectious agents, protein biomarkers for cancer, neurodegenerative disease and heart disease [Holland and Kiechle 2005, Soper et al 2006, Wang 2006].

2.2.14   Advanced home care technology

Introduction of new medical technology primarily takes place in (academic) hospitals. After several years of experience and adaptation, the technology is sometimes introduced in other settings such as the patients' home. In view of their expanded intended use, we still consider such technologies "emerging technologies".

The growing use of medical devices in less controlled environments, like the patients home, may imply (new) risks. To enhance patient safety at home it is of importance that devices are designed for use at home and have clear instructions for use. Organizational precautions that can be taken are employment of specialized nursing teams and a clear demarcation of the tasks and responsibilities of all parties that are involved in home care technology. Finally, instruction and monitoring of patients and informal carers must be part of technology enhanced-treatments.

A more extensive overview of developments in this area and related risks is provided in Appendix F of this report.

2.2.15   Combinations of the above

As pointed out before, an important trend is the combination of different technologies to build superior products. While this trend can already be recognized in a number of the examples in the preceding paragraphs, more extreme combinations are under development which should be taken into consideration.

An active implant may, for example, incorporate:
- advanced new "smart" materials aimed at improving biocompatibility or exerting some local effect on surrounding tissues
- pharmaceutically active substances
- biosensors with active feedback to the main device
- complex microelectronics and supporting software
- advanced battery technology aimed at extending the periods between implantation and explantation
- the facility to interface with remote devices via low power telemetry, enabling remote programming or monitoring
- use alongside complementary treatments, perhaps involving human cell and tissue engineering
- and may be implanted using state-of-the-art robotic assisted surgical procedures.

Another illustrative example is the development of multifunctional nanoplatforms for cancer diagnosis and treatment. Future efforts in cancer therapy are envisaged to be driven by multi-

functionality and modularity, i.e. creating functional modalities that can be assembled into nanoplatforms and can be modified to meet the particular demands of a given clinical situation. These nanoplatforms can be independently coupled to targeting and imaging modalities, and can selectively deliver therapeutics even intracellularly, after which the effectiveness of the treatment can be followed using monitoring modalities, see also Figure 2.2. Thus, the approach may allow for interchangeable therapeutic nanoplatforms enabling new refined non-invasive procedures that can potentially be more powerful than current treatment modalities, but are inherently more complex than existing small molecule or protein therapeutics [Roszek et al 2005].

It is anticipated that most efforts will generate products in clinical investigations or even in clinical use within five to ten years. More difficult technological and biological problems or the integration of multiple technological components will require at least five extra years but have the potential of making paradigm-changing impacts on detection, treatment and prevention of cancer. However, dendrimer-based nanoplatforms capable of delivering drugs and genes to specific targeted cells with imaging/monitoring modality are expected to enter clinical investigations within 3 years [NanoCure™ Corporation (Ann Arbor, Michigan, USA)].

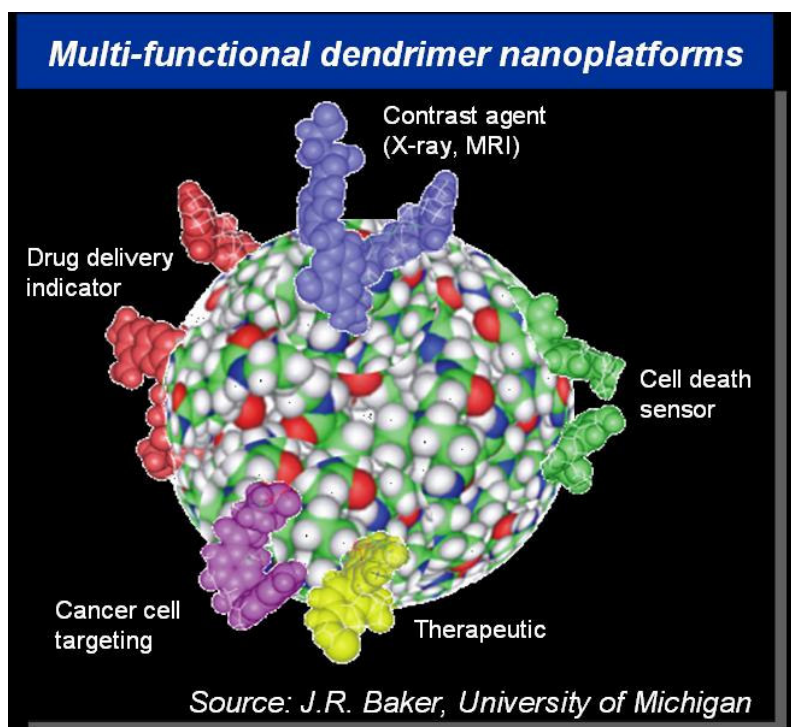*Figure 2.2: Nanoplatform combining modalities for targeting, imaging, therapy and monitoring of cancer diagnosis and treatment.*

2.3 References

Aoki J, Serruys PW, van Beusekom H, et al. Endothelial progenitor cell capture by stents coated with antibody against CD34: the HEALING-FIM (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth – First In Man) Registry. J. Am. Coll. Cardiol. 2005; 45: 1574-1579.

Babapulle MN, Joseph L, Bélisle P et al. A hierarchical Bayesian meta-analysis of randomised clinical trials of drug-eluting stents. Lancet 2004; 364: 583-591.

Benabid AL, Pollak P, Gao D et al. Chronic electrical stimulation of the ventralis intermedius nucleus of the thalamus as a treatment of movement disorders. J. Neurosurg. 1996; 84: 203-214.

Bose D, Eggebrecht H, Haude M et al. First absorbable metal stent implantation in human coronary arteries. Am. Heart Hosp. J. 2006; 4: 128-130.

Brown JA, Lutsep H, Cramer SC et al. Motor cortex stimulation for enhancement of recovery after stroke: Case report. Neurol. Res. 2003; 25: 815-818.

Cherry SR. The 2006 Henry N Wagner Lecture: Of mice and men (and positrons) – advances in PET imaging technology. J. Nucl. Med. 2006; 47: 1735-1745.

Cunningham AS, Harding S, Chatfield DA, et al. Metallic neurosurgical implants for cranial reconstruction and fixation: assessment of magnetic field interactions, heating and artifacts at 3.0 Tesla. Br. J. Neurosurg. 2005; 19: 167-172.

Edwards van Muyen A. Trends in medical technology: functional imaging. Medisch Nieuws 2006; 2: 21-24.

European Commission - DG Enterprise. Medical devices guidance document – Demarcation between: Directive 90/385/EEC on active implantable medical devices. Directive 93/42/EEC on medical devices, and Directive 65/65/EEC relating to medicinal products and related directives. MEDDEV 2.1/3 rev.2, July 2001. Available from: http://ec.europa.eu/enterprise/medical_devices/meddev/2_1_3____07-2001.pdf . Accessed December 29, 2006.

European Commission - DG Enterprise. Advanced therapies: tissue engineering, cell therapy and gene therapy. 16 November 2005. Available from: http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/index.htm . Accessed December 29, 2006.

GHTF Study Group 1. Information document concerning the definition of the term "Medical Device". Available from: http://www.ghtf.org/sg1/inventorysg1/sg1n29r162005.pdf. Accessed December 29, 2006.

Grube E, Sonoda S, Ikeno F et al. Six- and twelve month results from First human experience using everolimus-eluting stents with bioabsorbable polymer. Circulation 2004; 109: 2168-71.Guthberlet M. Viewpoint: the way forward in cardiac imaging. Circulation 2006; August 1: f117-f118.

Heublein B, Rohde R, Kaese V et al. Biocorrosion of magnesium alloys: A new principle in cardiovascular implant technology? Heart 2003; 89: 651-656.

Hochberg LR, Serruya MD, Friehs GM et al. Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature 2006; 442: 164-171.

Hodgson JM, Stone GW, Lincoff AM et al. Late stent thrombosis: Considerations and practical advice for the use of drug-eluting stents: A report from the society for cardiovascular angiography and interventions drug-eluting stent task force. Catheter Cardiovasc Interv 2007, online publication. Accessed January 30, 2007. Holland CA, Kiechle FL. Point-of-care molecular diagnostic systems – past, present and future. Current Opinion in Microbiology 2005; 8: 504-509.

Horger M, Bares R. The role of single photon emission computed tomography/computed tomography in benign and malignant bone disease. Semin. Nucl. Med. 2006; 36: 286-294.

Huckle D. Point-of-care diagnostics: will the hurdles be overcome this time? Expert Rev. Med. Devices 2006; 3: 421-426.

Jong WH de, Roszek B, Geertsma RE. Nanotechnology in medical applications: Possible risks for human health. RIVM report 265001001, 2005. RIVM, National Institute for

Public Health and the Environment, Bilthoven, The Netherlands, 2005. Available from: http://www.rivm.nl/bibliotheek/rapporten/265001002.html . Accessed December 29, 2006.

Lodge MA, Braess H, Mahmoud F et al. Developments in nuclear cardiology: transition from single photon emission computed tomography to positron emission tomography-computed tomography. J. Invasive Cardiol. 2005; 17: 491-496.

McFarland DJ, Sarnacki WA, Vaughan TM et al. Brain-computer interface (BCI) operation: signal and noise during early training sessions. Clin. Neurophysiol. 2005; 116: 56-62.

Moreno R, Fernández C, Hernández R et al. Drug-eluting stent thrombosis. J. Am. Coll. Cardiol. 2005; 45: 954-959.

O'Connor MK, Kemp BJ. Single photon emission computed tomography/computed tomography: basic instrumentation and innovations. Semin. Nucl. Med. 2006; 36: 258-266.

Ormiston JA, Webster MWI, Armstrong G. First-in-human implantation of a fully bioabsorbable drug-eluting stent: The BVS poly-L-lactic acid everolimus-eluting coronary stent. Catheter. Cardiovasc. Interv. 2007; 69: 128-131.

Persson A. Imaging technology of the future. Br. J. Surg. 2006; 93: 1182-1184.

Roszek B, Jong WH de, Geertsma RE. Nanotechnology for medical applications: state-of-the-art in materials and devices. RIVM report 265001001, 2005. RIVM, National Institute for Public Health and the Environment, Bilthoven, The Netherlands, 2005. Available from: http://www.rivm.nl/bibliotheek/rapporten/265001001.html . Accessed December 29, 2006.

Schmidt GP, Haug AR, Schoenberg SO, Reiser MF. Whole-body MRI and PET-CT in the management of cancer patients. Eur. Radiol. 2006; 16: 1216-1225.

Schrom T, Thelen A, Asbach P, Bauknecht HC. Effect of 7.0 Tesla MRI on upper eyelid implants. Ophthal. Plast. Reconstr. Surg. 2006; 22: 480-482.

Seemann MD. Whole-body PET/MRI: the future in oncological imaging. Technol. Cancer Res. Treat. 2005; 4: 577-582.

Shellock FG. Metallic neurosurgical implants: evaluation of magnetic field interactions, heating and artifacts at 1.5 Tesla. J. Magn. Reson. Imaging 2001; 14: 295-299.

Shellock FG, Forder JR. Drug eluting stent: in vitro evaluation of magnetic resonance safety at 3 Tesla. J. Cardiovasc. Magn. Reson. 2005; 7: 415-419.

Skalak R and Fox C, editors. Tissue engineering. Proceedings of a workshop held at Granlibakken, Lake Tahoe, CA, Feb 26-29, 1988. New York, NY: Liss; 1988.

Soper SA, Brown K, Ellington A, et al. Point-of-care biosensor systems for cancer diagnostics/prognostics. Biosens. Bioelectron. 2006; 21: 1932-1942.

Strauss HW. Nuclear Medicine 2020. Q. J. Nucl. Med. Mol. Imaging 2006; 50:1-3.

Thelen A, Bauknecht HC, Asbach P, Schrom T. Behavior of metal implants used in ENT surgery in 7 Tesla magnetic resonance imaging. Eur. Arch. Otorhinolaryngol 2006; 263: 900-905.

Tienhoven EAE van, Geertsma RE, Wassenaar C, Jong WH de. Pre-clinical safety assessment of Tissue Engineered Medical Products (TEMPs) -An investigation on assays and guidelines for biocompatibility testing. RIVM report 640080002, 2001. RIVM, National Institute for Public Health and the Environment, Bilthoven, The Netherlands, 2001. Available from: http://www.rivm.nl/bibliotheek/rapporten/640080002.html . Accessed December 29, 2006.

Tienhoven EAE van, Wassenaar C. Safety of human tissues and disease transmission: An inventory of guidelines (in Dutch). RIVM report 605148010, 2002. RIVM, National Institute for Public Health and the Environment, Bilthoven, The Netherlands, 2002.

Available from: http://www.rivm.nl/bibliotheek/rapporten/605148010.html . Accessed December 29, 2006.

Townsend DW, Carney JPJ, Yap JT, Hall NC. PET/CT today and tomorrow. J. Nucl. Med. 2004; 45: 4S-14S.

Wagenaar DJ, Kapusta M, Li J, Patt BE. Rationale for the combination of nuclear medicine with magnetic resonance for preclinical imaging. Technol. Cancer Res. Treat. 2006; 5: 343-350.

Wang J. Electrochemical biosensors: towards point-of-care cancer diagnostics. Biosens. Bioelectron. 2006; 21: 1887-1892.

Wassenaar C, Geertsma RE, Kallewaard M. Tissue engineered medical products. A prelude to risk management. RIVM report 605148009, 2001. RIVM, National Institute for Public Health and the Environment, Bilthoven, The Netherlands, 2001. Available from: http://www.rivm.nl/bibliotheek/rapporten/605148009.html . Accessed December 29, 2006.

Wolpaw JR, Birbaumer N, McFarland DJ et al. Brain-computer interfaces for communication and control. Clin. Neurophysiol. 2002; 113: 767-791.

Zaidi H. Recent developments and future trends in nuclear medicine instrumentation. Z. Med. Phys. 2006; 16: 5-17.

3.   Existing regulation in relation to emerging technologies

3.1   General

The existing regulatory frameworks for marketing authorisation of medicinal products, medical devices, in-vitro diagnostics and combination products show differences, in particular with regard to the amount of direct control that is exerted by the authorities. Medicinal products are regulated by the Medicinal Products Directive [1]. An application has to be made with the European Medicines Evaluation Agency in London or with a national competent authority for medicinal products, depending on the type of product. After an assessment procedure, during which a dialogue with the manufacturer usually takes place, registration implying market approval may be achieved if all concerns from the authorities have been addressed appropriately.

Medical devices are regulated by the Medical Device Directive (MDD) [2], the Active Implantable Medical Device Directive (AIMDD) [3] and the In vitro Diagnostic Devices Directive (IVDD) [4]. A specified conformity assessment procedure has to be followed to demonstrate compliance of a certain medical device with the Essential (Product) Requirements described in the directives. After successful completion of this procedure, the CE (Conformité Européenne) mark can be affixed to the product. Once a medical device has been granted a CE mark in one Member State, it can be freely marketed within the entire EEA. Depending on the risk classification of the device, more or less involvement of a Notified Body is required during the conformity assessment procedure. A Notified Body is an independent commercial organisation, which is accredited and surveyed by national competent authorities.

On 16 November 2005 the European Commission adopted a proposal for a Regulation of the European Parliament and of the Council on advanced therapy medicinal products (ATP), in particular related to tissue engineering, cell therapy and gene therapy [5]. The proposal aims to resolve the current regulatory gap in this emerging field by addressing all advanced therapy products within a single, integrated and tailored framework. This proposal is based on extensive consultation of all stakeholders, and a comprehensive impact assessment. It will be forwarded to the European Parliament and Council, for co-decision.

At the moment the MDD is under review [6]. The two council working groups dealing with the ATP and MDD are working closely together in order to make sure that the resulting regulation will be consistent and comprehensive.

As described in this report, new generations of medical technology products increasingly cut across traditional regulatory boundaries between medical devices, pharmaceutical products or human tissues. This will lead to an increasing number of products that may be hard to classify. Several years ago, the European Commission installed a Borderline/Classification Working Group and issued a guidance document on the demarcation between medical devices and medicinal products [7]. This document describes classification of borderline products and drug device combination products, including the regulatory pathways that should be followed. While the European regulations on combination products utilizing live human or animal cells are still under development [5], guidance for borderline products utilizing cells is not yet available.

European medical devices directives require that the devices must be designed and manufactured in such a way that, when used under the conditions and for the purposes intended, they will not compromise the clinical condition or the safety of patients, or the safety and health of users or, where applicable, other persons, provided that any risks which may be associated with their use constitute acceptable risks when weighed against the benefits to the patient and are compatible with a high level of protection of health and safety [2]. In selecting the most appropriate solutions for the design and construction of the devices, these solutions must conform to safety principles, taking account of the generally acknowledged state of the art, and the manufacturer must apply the following principles in the following order:

- eliminate or reduce risks as far as possible (inherently safe design and construction),
- where appropriate take adequate protection measures including alarms if necessary, in relation to risks that cannot be eliminated,
- inform users of the residual risks due to any shortcomings of the protection measures adopted.

In this context, 'eliminating' or 'reducing' risk must be interpreted and applied in such a way as to take account of technology and practice existing at the time of design and of technical and economical considerations compatible with a high level of protection of health and safety.

One means of complying with the above requirements is to implement a risk management system. The principles of such a system are described in 3.2.

For emerging technologies with their specific, possibly new and partly unknown risks, the question has been asked whether the existing regulations for the different types of medical products are sufficient to guarantee the safe use of these technologies in practice. Depending on the type of risks identified for a certain technology, national competent authorities may wish to consider additional regulatory measures. Examples of possible regulatory solutions are described in 3.3.

3.2   Short introduction to risk management

In order to guarantee the safe application of any technology, the associated risks need to be managed. In EN-ISO 14971 "Medical-Devices- Risk Management - Application of risk management to medical devices", the process of risk management is defined as the systematic application of management policies, procedures and practices to the tasks of analysing, evaluating and controlling risk [8]. Risk management is a continuous process, described as a set of repeatable steps throughout the entire life cycle of medical devices, re-evaluation of all steps in this iterative process being essential. With regard to the safe application of new and emerging medical technologies, various stakeholders are involved, including manufacturers, competent authorities and/or designated bodies, health care providers, and health care users (patients).

During the risk management process, stakeholders identify each hazard, evaluate the risks, and implement and verify risk control measures one at a time. On top of this there is a need to step back, add up all the individual residual risks, and decide on the acceptability of risks and the need and possibility for further risk reduction: the overall risk evaluation. Risk evaluation is a judgement of whether a risk is acceptable, based on risk analysis and the current values of society. It is possible that the overall residual risk can exceed the stakeholders' criteria for acceptable risk, even though individual risks do not.

The primary user of the risk evaluation and risk management is the manufacturer, because it is this party that is placing the product on the market and therefore has the obligation to ensure quality, including safety. However, a systematic approach to analysis, evaluation and

control of safety problems may also be of use to other parties such as regulatory authorities. Risk assessment is at the basis of the risk management in answering the question whether there are potential risks involved with the use of a medical technology. As we are dealing with medical applications estimation of benefit is an important part of the risk assessment. If a manufacturer judges the overall residual risk to be acceptable in relation to the expected benefit of their product, taking also into account a comparison to available alternatives, the marketing phase can be entered.

According to current regulations for most medical products, regulatory authorities and/or designated independent bodies (e.g. Notified Bodies) decide on the acceptability of the overall residual risk of the product by assessing the scientific evidence on safety and performance/efficacy as provided by the manufacturer. If the safety and performance/efficacy is deemed acceptable, market authorisation can be granted. It is important to realize that deciding on risk acceptability by manufacturers and authorities is an ongoing, iterative process. Once new information becomes available, for example in the post-production phase, the acceptability of risk should be re-evaluated.

3.3   Possible regulatory solutions

Part of the new and emerging technologies could well be covered adequately by the current regulatory system, and for other technologies some amendments may be considered necessary. If problems were to be identified in the medical devices regulations, several possibilities exist to deal with this, ranging from introducing new regulation to providing appropriate guidance. Examples of regulatory solutions that can be considered are the following:

- developing a separate directive for a specific category of devices;
- amending existing directives with regard to specific categories of devices;
- adaptation of Essential Requirements;
- special classification rules for certain product categories;
- special requirements for clinical investigations with certain product categories.
- modified system for monitoring / vigilance;
- guidance on regulatory pathways for specific product categories;
- new mandates for standardization, e.g. a review of certain existing standards;

It is stressed that these are mere possibilities; specific proposals will need to be developed systematically for each category of devices where potential problems are identified.

3.4   References

[1] Medicinal Products Directive 2001/83/EC, Council Directive of 6 November, 2001. Available from: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol-1/dir_2001_83/dir_2001_83_en.pdf . Accessed January 24, 2007.

[2] Medical Devices Directive 93/42/EEC, Council Directive of 14 June, 1993. Available from: http://eur-lex.europa.eu/LexUriServ/site/en/consleg/1993/L/01993L0042-20031120-en.pdf. Accessed December 11, 2006.

[3] Active Implantable Medical Devices Directive 90/385/EEC, Council Directive of 20 June, 1990. Available from:

http://eur-lex.europa.eu/LexUriServ/site/en/consleg/1990/L/01990L0385-19930802-
en.pdf. Accessed December 11, 2006.

[4] In Vitro Diagnostic Medical Devices Directive 98/79/EEC, Council Directive of 27
October, 1998. Available from:
http://eur-lex.europa.eu/LexUriServ/site/en/consleg/1998/L/01998L0079-19981207-
en.pdf. Accessed December 11, 2006.

[5] European Commission DG Enterprise. Advanced therapies: tissue engineering, cell
therapy and gene therapy. Available from:
http://ec.europa.eu/enterprise/pharmaceuticals/advtherapies/index.htm . Accessed
December 29, 2006.

[6] European Commission, Public Consultation Text, 5 April 2005. Draft Commission
Proposal, Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.
Available from:
http://ec.europa.eu/enterprise/medical_devices/consult_docs/Public_Consultation_draft.p
df. Accessed December 11, 2006.

[7] European Commission DG Enterprise. Medical devices guidance document –
Demarcation between:
- Directive 90/385/EEC on active implantable medical devices
- Directive 93/42/EEC on medical devices
and
- Directive 65/65/EEC relating to medicinal products
and
- related directives
MEDDEV 2.1/3 rev.2, July 2001. Available from:
http://ec.europa.eu/enterprise/medical_devices/meddev/2_1_3____07-2001.pdf .
Accessed December 29, 2006.

[8] EN ISO 14971:2000 Medical devices – Application of risk management to medical
devices. + Amendment 1:2003. Rationale for requirements. CEN, Brussels, Belgium,
2000/2003.

4. Discussion and Conclusions

This report describes developments in new and emerging technologies, as well as innovative applications and modifications of existing technologies. These will have great impact on the quality of care that can be delivered to patients and the location in which that care is delivered. The report does not aim to cover the entire range of rapidly emerging medical technologies. However, it does give a broad outline of a significant part of those technologies that are relevant for decision makers. Moreover, it describes six categories of products in more detail.

The scope of this report is limited to products that classify as medical devices, however, this borderline proves to be difficult to maintain. New generations of medical technology products increasingly result from so-called "converging technologies", i.e. the combination of different technologies which leads to the crossing of borders between traditional categories of medical products such as medical devices, pharmaceutical products or human tissues. Combined with the development and perfection of minimally-invasive surgical techniques, these new generations of devices offer patients improved treatments, better prognosis and reduced recovery times.

Apart from the growing number of borderline products and combination products, the trend can be observed that a growing number of illnesses and disorders can be treated with technological solutions instead of medicines. An example is the treatment of previously inoperable cancer types by local minimally invasive surgery or locally applied radiation using sophisticated imaging techniques during the intervention, while the only solution used to be chemotherapy with severe side effects. Also in cardiology, nowadays implantable devices are used to support patients suffering from for example arrhythmia which used to be treated with medication, and stroke patients may benefit from a surgical removal of a blood clot instead of using a medicine to dissolve it.

As well as benefits, these technological developments inherently bring new challenges and new risks, especially because of the convergence of different technologies.

Generally, the risks associated with emerging technologies may be related to the following:

- Emerging technologies may introduce new aspects intrinsic to the (design of the) devices, such as the use of new materials with new, sometimes unknown properties, or the construction of increasingly complex devices with a higher risk of failure.
- Combinations of different technologies on the one hand may fail to interact where necessary and even hardware and/or software systems using similar technology will not always communicate correctly unless all components come from the same manufacturer. On the other hand, unintended interaction might also occur.
- Technology systems taking over control imply a longer period before a severe or fatal deviation in device functioning is detected and appropriate action can be taken; moreover, failures of technology which takes over more vital body functions will result in more severe consequences.
- Increasing complexity leads to a technology gap for clinicians. Bridging the gap is difficult because engineers responsible for the technology and clinicians using it speak different languages. This causes a higher risk of use error and fewer possibilities to correct these.

-     For new and emerging technologies, specific training of users is of essential importance in order to get the desired performance level and to avoid use errors. This is not included in the traditional education of medical professionals and it has been established that most technologies show a clear learning curve.
-     Elevated risk levels result from the diffusion of advanced technology from highly controlled hospital environments to point of (primary) care or even to home situations where users are less thoroughly trained and the level of control is considerably lower.

Considering these aspects, it is important to realise that previous generations of medical devices were very much a product of "traditional" engineering technologies with straightforward engineering problems. Medical devices tended to fall into distinct categories such as surgical, diagnostic or active implantable. With the advent of the new categories of products, where technologies are increasingly being combined and used in an integrated fashion, it is becoming more and more important that risks are evaluated by multidisciplinary teams applying well established principles of risk management, like they are described for example in the European standard EN ISO 14971. This is necessary to ensure that risks related to different technology aspects are being covered adequately. In addition, such a team should consider the effect that interaction of different components might have on the generation of new risks. One should realize that for risk estimation of such products simple arithmetic is no longer valid, i.e. the risks related to the combination product may not be equal to the simple sum of the risks related to the constituting components.
Obviously, training and education with regard to new technologies needs to be given a large focus of attention. In addition to traditional training methods, computer-based simulators will increasingly be more eligible as a training aid, especially due to their extensive assortment of educational features such as video databases, 3D-anatomical atlas, multimedia presentations and video conferences from 'live' procedures. Also, a database that includes recordings from the training sessions provides valuable statistical information on a per user basis. Training with computer-based simulators is a novel approach with versatile educational potentials that might motivate physicians to improve their skills and better assess new techniques beforehand instead of trusting their improvising talents.
Furthermore, there may be a need for a new type of health care professional, dedicated exclusively to the well functioning of sophisticated technology during clinical procedures. We could call this person a clinical technician. This person needs a clinical as well as a technical background. His/her competence is the determinant factor in operative time and safety of the procedure. In addition, introduction of a substantial technical component in the curricula for medical specialists can be highly recommended.

For emerging technologies with their specific, possibly new and partly unknown risks, the question has been asked whether the existing regulations for the different types of medical products are sufficient to guarantee the safe use of these technologies in practice.
It is considered a challenge for all stakeholders to deal with these risks in such a way that patient safety is guaranteed. Governments recognise the important role of product design in ensuring patient safety and are working with all stakeholders to find ways of providing constructive feedback to manufacturers on issues of both product design and manufacturing practices. In addition to this, alarm, monitoring and back-up systems are advocated as important tools.
It is being evaluated whether the new or increased risks of emerging technologies call for any amendments of current regulations. On the other hand, innovation should not be hampered unnecessarily and the availability of innovative technologies to patients should not be jeopardized.

Given the fact that existing regulations for all medical technology applications require the implementation of a risk management strategy by the manufacturer, most if not all new risks related to emerging medical technologies should be covered. Well performed risk assessment should result in the recognition of new or additional risks, which will subsequently be controlled. Any initially unrecognised risks will be identified by an active post market surveillance system and this information will be fed back into the risk assessment.
For some categories of emerging medical technologies it may, however, be advisable to develop guidance or standards at a European level, pointing out new or increased risks and proposed control measures to relevant stakeholders. In addition, the implementation aspects of the existing regulations, such as classification of products, might need amendments.

Apart from specific guidance, also the more generally applicable existing European Commission guidance document on the demarcation between medical device and medicinal products [1] should probably be revised. This document, published in 2001, needs an update in view of the increasing numbers of combination products, and in order to include the third category of human cells and tissues. European regulations are building towards a triangle without gaps or overlaps. This will only work if clear and updated guidance is also provided. See Figure 9.1 for an illustration of this problem.
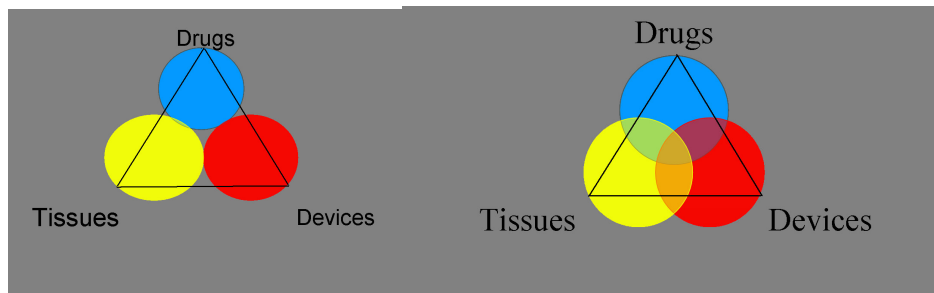
Figure 9.1: Triangle of medical products: separate categories (left) converging towards growing numbers of combination products (right) – a challenge for regulation

Specific consideration should also be given to the observation that proper risk management with regard to emerging technologies generally requires specific education and training of the users. At a recent conference on patient safety in the Netherlands, the majority of people attending a workshop on the risks of new and emerging technologies were in favour of introducing a sort of license for medical professionals who would like to use such technologies. This proposed technology-specific license should be obtained only if sufficient training were followed. The difficult question who would be responsible for organizing and implementing systems for sufficient training and possibly licensing surgeons for specific new technologies was not solved during the workshop. Can manufacturers be held responsible for organizing this based on the fact that a thorough risk assessment of their product would indicate that use errors should be controlled in part by providing a training? Could such a requirement be enforced based on product regulations such as the Medical Devices Directive? Or would training and education have to be covered by different regulations, and what exactly is the role of the national competent authority in this matter?

It is recommended that all of the abovementioned issues related to risk management and regulation of emerging technologies including requirements for training and education are discussed at a European level and with all stakeholders.

Appendix A: Minimally invasive surgery

A.1 Introduction

Minimally invasive surgery (MIS) techniques seek to perform surgical procedures through minimal access wounds, thereby avoiding the morbidity of conventional surgical wounds. This became possible through a combination of technological advances. The development of the innovative lens systems and the miniaturisation of video cameras allowed the surgeon visualisation inside the body at least equal to open surgery. Furthermore, insufflation devices allowed controlled distension of body cavities with gas to provide the surgeon space to work.

MIS is typically an example of a technology that is not new, however, it can be considered an emerging technology because of the constant innovation which leads to a rapidly increasing number of possible interventions. Advancements in the last ten years have made it possible to perform a surgical procedure without directly visualizing or touching the organ being operated on. Efforts are now focused on those techniques that facilitate the more complex tasks by minimally invasive approaches. Technologies that will impact surgery include those that allow procedures to be performed through natural orifices, e.g. for esophageal reflux disease and those with flexible miniaturized instruments capable of delivering sutures, clips, or energy sources for excising or shrinking tissue. Computer-assisted surgery systems will continue to evolve and will probably get their place in the operation room of the future. Developments in the remote delivery of focused energy (e.g. ultrasound and radiation) under image guidance (e.g. magnetic resonance imaging and ultrasound) will permit the ablation of tumors of the prostate, breast, liver, and lung without the need for an incision at all. Noninvasive approaches may potentially be used for ablating plaques in arteries, revascularizing the myocardium, treating tennis elbow, and nonunion fractures. Advancements in microchip and wireless technology may allow the development of microrobots for completing surgical procedures, and magnetically controlled implants that can be navigated remotely. {Mack MJ, 2001}

MIS provides a number of heavily advertised benefits to the different stakeholders who are involved in healthcare, see Figure A.1. However, each treatment must be evaluated with regard to the associated risks balanced against the evidence of the patient's benefit, surgical morbidity, short- and long-term outcome, cost effectiveness and maintenance of quality of life, compared with the competitive treatment methods.

In the following paragraphs, some of the developments in MIS are highlighted, as well the influence of these developments on the layout of the operating theatre and the education of the surgeons. These developments are derived from both scientific literature and from information found on websites from manufacturers, universities and clinics. Most of these are in a phase of field penetration. It is not certain whether these developments will grow into standard procedures and surgical techniques. As with all new developments, many of these sources focus on the marvels and virtually unlimited advantages of the novelties, mostly disregarding the risks involved with the introduction of the new techniques. Paragraph A.5 is therefore dedicated to the associated risks.

benefits of minimally invasive surgery

Employer
- Lower total cost of care
- Employees recover and return to work faster
- Improved productivity/lower replacement and overtime costs
- Value (quality/price)

Health Care Plans
- Reduced total health care costs to employers
- Improved clinical care
- Competitive differentiation
- Measurable quality improvements (NCQA HEDIS, FACCT)
- Member satisfaction

Patient
- Less scarring
- Shorter recovery times
- Faster return to normal activities
- Surgical options

Insurers
- Lower medical costs
- Improved clinical care
- Lower disability costs

Hospitals
- Reduced costs via reduced lengths of stay
- Improved clinical outcomes (quality)
- Leverage for improved reimbursement
- Differentiation
- Growth potential

Surgeons
- Better clinical outcomes
- Lower medical risks (improved quality)
- Differentiation and appeal to patients, MCOs, and employers

Figure A.1: Benefits of minimally invasive surgery (MIS)

A.2   Recent applications of MIS techniques

A.2.1 Cardiac surgery

Cardiac surgery has been the last of the surgical specialties to embrace the principles of MIS. The complexity and invasiveness of cardiac surgery procedures have presented both a problem and an opportunity to make them less invasive.

Although cardiac surgery has been performed more than 10 million times in the past 30 years with generally good results, splitting the sternum and spreading the rib cage to gain access to the heart is a cause for significant morbidity. The use of the heart-lung machine adds further morbidity, which is estimated to be higher than that of the sternotomy.

In the past decade, the face of cardiac surgery has been changed by a number of technological advances, most notably the development of less invasive techniques. Initial attempts to perform cardiac operations through small incisions were hindered by the absence of appropriate accessory technology, such as visualization systems, retractors, stabilizers, and alternate methods of vascular cannulation and cardiopulmonary bypass. With the development of these technologies, surgeons have become increasingly able to perform complex cardiac procedures, including coronary artery bypass, mitral and aortic valve replacement, and atrial septal defect closure, through smaller-than-traditional incisions. Nonetheless, in many cases, the extent to which incision size has been reduced has been matched by a corresponding increase in technical difficulty and operating time. For example, minimally invasive direct coronary artery bypass (MIDCAB), in which a single vessel bypass to the anterolateral surface of the heart is achieved through a small anterior mini-thoracotomy, requires internal mammary artery graft harvesting by thoracoscopy, which even in the most experienced hands is time consuming and technically challenging. Furthermore,

the decreased visualization through small thoracotomy incisions has led to a significant incidence of complications with this procedure.

Advances in the area of peripheral cardiopulmonary bypass access and endoaortic balloon technology (port-access) have allowed valve surgery and other open-heart procedures (such as atrial septal defect repair) to be performed through smaller-than-usual (but not necessarily small) incisions. The development of these procedures has required the adaptation of surgical instruments and techniques to the challenge of operating 'in a deep hole' with less than optimal visualization. For these and other technical reasons, these procedures have been performed predominantly at selected centres, and have not gained widespread popularity. Moving the surgical instruments manually during endoscopic surgery can be difficult - the instruments are far longer than normal, and the "feel" of these long instruments is non-intuitive to the surgeon. Long instruments also exaggerate normal hand tremors. Thus, endoscopic surgery has achieved only limited success in heart surgery, where the heart is beating and the necessary surgical manoeuvres tend to be complex.

Computer-assisted surgery systems have been developed, aimed at making endoscopic heart operations feasible. Using the surgical robot, surgeons can manipulate small instruments, which are inserted through small chest incisions, in tight spaces, achieving many of the technical manoeuvres previously possible only with open exposure.

The surgical robot combines computer technology and the surgeon's skill. It enhances the surgeon's ability to perform complex minimally invasive surgery, providing more precision, an increased range of motion, improved dexterity, and enhanced 3D visualization.

To use the surgical robot, the surgeon makes three small incisions in which he inserts the robotic arms; two arms hold surgical instruments and the third has a tiny video camera. The surgeon then sits at a computer console, where the camera transmits a 3-D magnified image. The surgeon places his hands in holders that control the robotic arms and performs the procedure while seated at the computer console.

In the field of minimally invasive cardiac surgery, robots can be used for:
-      Thoracoscopic internal mammary artery harvesting and subsequent MIDCAB,
-      Mitral valve surgery.
-      Atrial septal defect repair.
-      Arrhythmia ablation, using a variety of energy sources.

The potential significance of robotic technology in the practice of cardiac surgery is considered to be great. Robots have given a previously unimaginable degree of visualization and instrument dexterity. The technology that is available today is just an initial iteration of a complex developmental process. The continued evolution of robotic technology, toward the goal of widespread applicability, will require many more mechanical and engineering refinements {http://www.nyp.org/masc/davinci.htm}.

Mack, however, is not so enthusiastic about the necessity of robotic technology for minimally invasive procedures in cardiac surgery. Although robotics for e.g. limited-access mitral valve surgery has received some acceptance, many centers are capable of performing the procedure without robotic assistance {Mack, 2006}.

A.2.2 Endovascular Surgery

Endovascular surgery is done from within the blood vessel. It is used to treat the two major problems that can develop in blood vessels: an aneurysm (an abnormal blood-filled dilatation of a blood vessel) and a narrowing (also called occlusion or stenosis). The surgeon reaches the aneurysm or narrowing by inserting a catheter into a smaller artery, such as the femoral artery in the groin, and using x-ray imaging to advance it into the aneurysm or narrowing. To repair an aneurysm, the surgeon pushes a hollow graft with metal attachments through the

catheter to the aneurysm and anchors it in place. To open a narrowing, a balloon is inserted and advanced to the narrowing. The balloon is then inflated and a stent is expanded in the narrowing. The balloon is deflated and removed, and the stent keeps the artery open. Although stenting is not a new technology, the leading manufacturers keep on developing new variations and applications. For example, mitral valve repair by stent procedure is currently under clinical study in the Netherlands. A manufacturer of a stent coated with the drug Paclitaxel is investigating the safety and effectiveness of this new device to treat blockages above the knee in the major artery in the thigh (see Figure A.2). Peripheral arterial disease affects more than 30 million people worldwide. It develops most often as a result of the hardening of arteries (atherosclerosis), which occurs when cholesterol levels and/or scar tissue build up, causing the arteries to narrow and restrict blood flow. {http://www.zilverptxtrial.com/treatment.html}
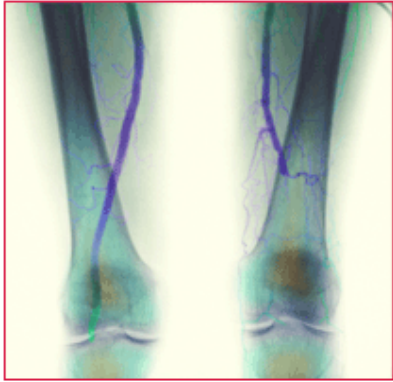
Figure A.2: Peripheral arterial blockage above the knee

A.2.3 Hernia repair

Bard has introduced a minimally invasive, tension-free hernia repair technique that can be completed through a small 4-6 cm incision. Minimal suturing is required which can result in less patient discomfort and minimize the risk of pain due to nerve damage. Since this repair can be performed using local or regional anesthesia, general anesthesia and its associated risks can be avoided. The repair is performed through an open, anterior approach, making it a simple repair for the majority of surgeons to learn and to perform. The modified kugel patch repair is claimed to provide the same benefits as a laparoscopic hernia repair in that the entire groin region is protected by the patch, thus reducing the risk of a recurrent or missed hernia. Additionally, a 'memory recoil' ring allows the patch to spring open and maintain its shape. A positioning strap and pocket facilitate positioning and fixation of the device for a stable permanent repair. {http://www.crbard.com/news/innovations/kugelpatch.cfm}
On the other hand, superior benefit in favour of laparoscopic hernia repair compared to open repair has been demonstrated only regarding a lower level of pain, a higher level of physical activity, and earlier return to work. However, in terms of operating time and costs, open repair without mesh has benefits. {Beger, 2002}

A.2.4 Spinal fusion

Traditional open spinal surgery for spinal fusion requires the surgeon to make a 4- to 6- inch incision over the area of instability, directly exposing the spinal vertebrae by stripping the overlying muscles away from the spine. Due to recent technical advancements a spinal fusion can be made through small, 1/2- to 1-inch incisions, greatly reducing surgical trauma to the back muscles and reducing blood loss. Progress in this technique has resulted in improved fusion rates, shorter hospital stays, and a more active and rapid recovery as compared to the traditional way. One of the most significant technical advances in this arena is frameless stereotactic imaging. Also known as surgical navigation, this technique combines the use of 3-D X-ray images and a computerized guidance system, which enable the surgeon to place bone screws through very small incisions. {Frontiers, 3rd quarter 2005}

A.2.5 Knee and hip arthroplasty

An example of a minimally invasive approach in hip joint replacement and hip resurfacing surgery was developed by UK-based surgeon Mr G Chana. The latter technique is achieved through a small posterior incision and has been acclaimed by patients, surgeons and hospital authorities. It affords a range of extensive benefits to a patient, including minimal blood loss, quicker recovery time, less pain and earlier discharge from hospital.
{http://www.minimalinvasivehip.com/}

The minimally invasive hip replacement is carried out through a small posterior incision. The incision in conventional hip replacement surgery is typically 25 – 30cms, with minimal invasive surgery, it is reduced to 5.5 – 9 cms in length. The procedure is of benefit for older patients facing conventional hip replacement and for younger patients who are not suitable for hip resurfacing. Implants for this procedure have been accepted by NICE (National Institution of Clinical Excellence, UK).

The hip resurfacing procedure, of particular benefit to those with arthritic hip conditions, is carried out through a 7-11 cm incision without the need to divide the gluteus maximus, which is a big advantage. It results in considerably reduced blood loss, leads to faster recovery and rehabilitation for the patient and almost eliminates the need for post operative blood. In time, this technique may lead to a significant reduction in average post operative patient days in hospital and thereby eventually result in huge savings for healthcare providers.
{http://www.iconhip.com/index.htm}

There is also a great deal of interest in minimally invasive total-knee replacement. Borrowing some of the concepts developed by total-hip surgeons, minimal-incision total-knee surgery has become popular. Early reports by several authors show some advantages to the less-invasive approach for total-knee replacement, and an increasing number of publications support that this can be performed safely. As an example, a small study (n=41) comparing a cemented Miller-Galante unicompartmental knee arthroplasty inserted with either minimally invasive surgery or with a standard exposure by Carlsson can be taken. The rehabilitation of patients operated through a small incision was faster, and there was a significant difference in days of hospitalization (P = .03). No statistically significant difference was found between the 2 groups regarding clinical or radiographic data after 2 years follow-up. {L.V. Carlsson, 2006}

The development of surgical navigation systems can contribute greatly to the success of minimally invasive hip and knee replacement operations by giving surgeons an exact three dimensional, computer-generated model of the patient's anatomy and the surgical instruments during the procedure. With the ability to verify and optimize bone resections intra-operatively, margins of errors are discovered and corrected during surgery. Before the surgery is over, doctors can fine tune the placement of the prosthesis and even study mobility and range of motion. Surgeons can achieve the main goal of perfect implant alignment without having to perform preoperational examinations or take radiation-intensive and expensive CT or MRI scans. Using such systems, results better than traditional procedures have been reported with smaller incisions and shorter recovery times. Examples of surgical navigation systems include VectorVision[®], OrthoPilot[®], and Stryker's Navigation Systems {http://www.brainlab.com/scripts/website_english.asp}, to {http://www.orthopilot.com/} {http://www.stryker.com/navigation/us/index.htm}

However, caution must be exercised. There are no long-term reports supporting the general concepts of minimally invasive hip and knee replacements and further study must be done to ascertain whether noted improved outcomes are due to improved patient education, pain management and rehabilitation, or to less-invasive surgical techniques. {Dalury, D.F., 2006}

A.2.6 Morbid obesity

With the growing concern about the health issues that come with overweight, especially the cases of morbid obesity, more interest is shown for surgical procedures that can help obese patients to loose excess weight. The adjustable gastric band is a silicone elastomer hollow ring filled with saline, which is placed around the upper part of the stomach by a minimally invasive procedure. This creates a new small stomach pouch, with the larger part of the stomach below the band. This way, the food storage area in the stomach is reduced. The band also controls the stoma (stomach outlet) between the two parts of the stomach. To change the size of the stoma, the inner surface of the band can be adjusted by adding or removing saline. The band is connected by a tube to an access port placed beneath the skin during surgery. Later, the surgeon can control the amount of saline in the band by piercing the access port through the skin with a fine needle.

The adjustable gastric band provides reduced risks of complications compared to other surgical interventions such as the gastric bypass.{http://www.lapband.com}

Figure A.3: Adjustable gastric band

A.2.7 Oncology

The acceptance of minimally invasive surgery for the management of oncologic disease has been slow because of initial fears regarding the effect of this new approach on the interaction between the patient and the tumor. Over the last years, substantial improvements have been made regarding technology and surgical experience in laparoscopy and minimally invasive procedures. Minimally invasive techniques are applied for staging, palliation and curative procedures in cancer patients. However, laparoscopic resection in curative intent for solid organ cancer is still under debate. Recently, new data have emerged that might help to solve some of these issues. A review of the literature regarding minimally invasive procedures in gastrointestinal and breast cancer patients learned that in gastrointestinal cancers and lymphoma, laparoscopy has become an invaluable staging tool. The sentinel lymph node concept was shown to be a minimally invasive technique offering sufficient staging with decreased morbidity in selected breast cancer patients. However, at this time sentinel node biopsy for gastrointestinal cancer is purely investigational. From the present data from randomized trials laparoscopic colon resections are technically feasible and can be performed safely with adequate short and long term results. Presently it is not possible to make a general recommendation for laparoscopic rectal or gastric resections; no randomized trials are available. {Tausch C, 2006} Flexible endoscopes are providing additional opportunities for minimally invasive treatment of tumours (see paragraph A.3.1).

Another minimally invasive alternative to traditional surgery is presented by ablation techniques, which are applied by using the skills of interventional radiologists in using imaging guidance to deliver targeted cancer treatments throughout the body through the blood vessels or other pathways. Tumours can be killed locally with heat using radiofrequency ablation (RFA), laser, microwave thermotherapy or by freezing the tumour (cryoablation), without harming the healthy cells in the body. These techniques can provide options for patients who are not good surgical candidates, and thus may have a bad prognosis. Furthermore, repeat treatments in case new tumours are detected during follow-up are much easier to accomplish. See Figure A.4.
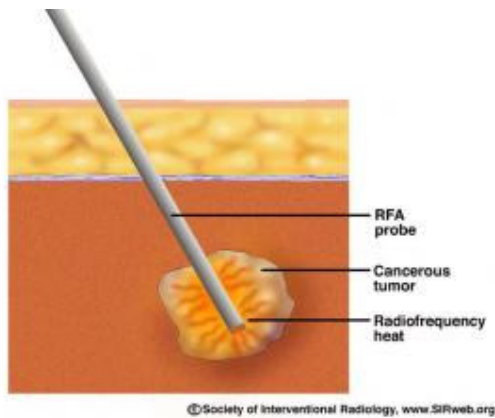{http://www.sciencedaily.com/releases/2005/11/051128081619.htm}

Figure A.4: RFA probe inserted into tumor to heat and kill tumor.

For example, RFA has been presented to be as effective as surgery to treat single small cell hepatocellular carcinoma (liver cancer) in a study of 162 patients, in terms of overall survival and rate of tumor recurrences. A study assessing survival in patients with small solitary colorectal liver metastasis treated with RFA shows that their survival was extremely good, with 3 and 5 year survival after ablation of 65% and 43% respectively. {http://www.sirweb.org/news/newsPDF/IR2oncologyfinal.pdf}

RFA is also claimed to be a safe, minimally invasive tool for local pulmonary tumour control with negligible mortality. A prospective trial in 106 patients receiving RFA to heat and kill their lung tumour, shows 91% cancer-specific survival at 2 years. The RFA technique successfully killed the tumour inside the lung without surgery in 93% of the cases. {http://www.sirweb.org/news/newsPDF/IR2oncologyfinal.pdf}

Laser ablation can, for example, be used to treat tumours that occur in both halves of the liver, which is practically impossible in a traditional surgery where typically only the left or right lobe is resected. Laser ablation was also presented as holding advantages over RFA, because it can be applied to different parts of the liver simultaneously, while RFA can only treat one tumour at a time and cannot be used with continuous MR monitoring. {http://www.mtbeurope.info/news/2005/512026.htm}

Microwave thermotherapy has been successfully applied to treat benign prostate hyperplasia. In a 12-month follow up of a randomized multi-center study involving 146 patients, 17% of patients undergoing TURP (transurethral resection of the prostate) experienced a serious adverse event while only 2% of the minimally invasive treatment group experienced a serious adverse event. {http://www.pharmacychoice.com/News/article.cfm?Article_ID=4718}

A prospective study of MRI-guided cryoablation of 44 renal tumours shows that 96% were successfully ablated and 93% required only one treatment session. When the iceball completely covers the tumours, there were no reoccurrences. {http://www.sirweb.org/news/newsPDF/IR2oncologyfinal.pdf}

A.2.8 Treatment for stroke

It is estimated that ischemic strokes account for 80% of the 700,000 strokes that occur each year. The standard treatment option is a clot-busting drug such as TPA. However, only one percent of patients actually use the drug, largely because it must be given within three hours of the onset of a stroke. Also, TPA cannot be used in patients who have recently undergone surgery, because it can cause heavy bleeding in the brain. The Merci® Retriever is an innovative FDA-approved device which can be used to remove blood clots from the brain in patients experiencing ischemic stroke. It can be used within eight hours of stroke onset, also on patients who have recently undergone surgery. In addition, doctors can perform the procedure in as little as 20 minutes, while TPA can take an hour or more to dissolve a clot. The device allows surgeons to go up inside the blood vessel that is blocked, directly to the site of the problem, and pull the clot out. It consists of a long, thin wire that is threaded

through a catheter into the blood vessel. The wire is made of a special alloy. It is pushed through the end of the catheter and it reshapes itself into tiny loops that latch onto the clot and pull it out. To prevent the clot from breaking off, a balloon at the end of the catheter inflates to stop blood flow through the artery. Previously, no tool was available that was strong
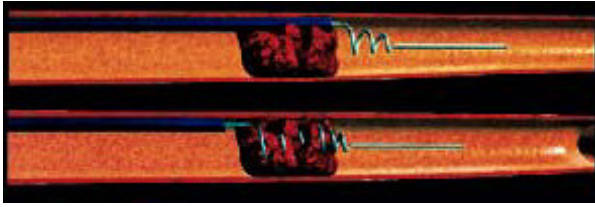
enough to remove a clot without tearing blood vessel walls. With this new device there still is a risk of damaging the walls of blood vessels, which can cause bleeding in the brain. {http://www.carolinaneurosurgery.com/vascular/merci.html}
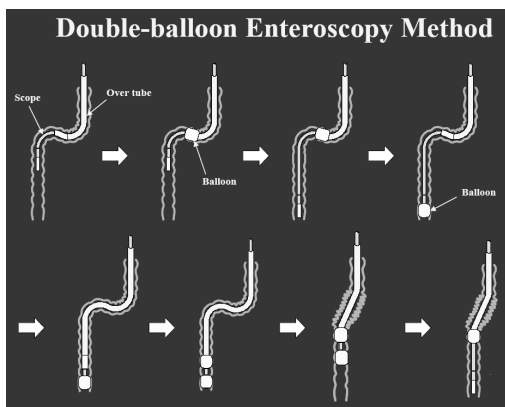
Figure A.5: Merci® Retriever for stroke treatment

A.3　Developments in surgical techniques and medical devices

A.3.1 Flexible endoscopic surgery

Flexible endoscopy has evolved from a diagnostic tool practiced predominantly by gastroenterologists to a minimally invasive surgical tool. Therapeutic endoluminal procedures are already becoming standard for many gastric, biliary, pancreatic and colonic maladies. New technologies are under investigation for endoscopic treatment of gastroesophageal reflux, morbid obesity, and ablation of premalignant tissue. In the future, flexible endoscopes may play a role in 'natural orifice' surgery, performing operations through the mouth or rectum without the need for external incisions. {J. L. Ponsky, 2006}

Flexible endoscope-based endoluminal and transgastric surgery (FES) for cholecystectomy, appendectomy, bariatric, and antireflux procedures show promise as a less invasive form of surgery. Current endoscopes and instruments are often inadequate to perform such complex surgeries for a variety of reasons: they are too flexible and are insufficient to provide robust grasping and anatomic retraction. A new articulating flexible endoscopic system was developed which passes through an incision in the wall of the stomach and can be manipulated in the peritoneal cavity. The device enables the surgeon to stiffen the flexible endoscope once it has been positioned, while still allowing full mobility of the tip. This device allowed effective transgastric exploration and procedures in the abdominal cavity including retraction of the liver and stomach to allow exposure of the gallbladder, retraction of the cecum, manipulation of the small bowel and exposure of the esophageal hiatus. The appeal of transgastric FES may not be immediately apparent, compared to the more-or-less mainstream acceptance of laparoscopic surgery. FES theoretically offers benefits: no incision through the skin and muscle of the abdomen, less pain, better cosmetic results, no general anesthesia, lower physiologic stress, and possibly reduced procedure costs. The greatest hurdle between studies and eventual human clinical use is closure of the gastric exit site. The gastrotomy represents a new source of potential complication and, as such, problems must be extremely rare or they will offset any advantage gained by the FES transgastric approach. There are currently several endoscopic suturing devices either available or in development. Further development of a closure device or method is imperative. {Swanstrom LL, 2005}{http://www.news-medical.net/?id=3133}

Another area with recent innovations is the small intestine, the most difficult organ of the digestive tract to diagnose and treat via endoscopy due to its extraordinary length and limited accessibility. The Double Balloon Endoscopy technology effectively stretches or 'pleats' the small intestine between two balloons, allowing the physician to examine and treat the entire length. Capsule endoscopy, using a miniature wireless video camera swallowed by the patient, allowed physicians to diagnose unexplained bleeding, Crohn's disease and other diseases of the small intestine. The development of this new system could mean that patients no longer have to undergo lengthy and complicated surgeries to treat these diseases. {http://community.ebaptisthealth.com/archives/2005/0331_DoubleBalloon.html}

Figure A.6: Double-balloon enteroscopy method

Fiberoptic telescopes can also be used for sinus and nasal surgery. The removal of chronically infected sinus tissue allows for proper drainage of the sinuses, relieving the pain, pressure, headaches, and recurrent infections associated with chronic sinusitis. Many sinus and nasal tumors, which previously required open surgical procedures, are amenable to removal using an endoscopic approach. A computerized image guidance system such as GE Insta-Trak® or Stryker Navigation Systems can be used, enabling the surgeon to perform a safer, more thorough operation without damaging critical surrounding structures like arteries and nerves, especially in difficult cases and when working in areas that are too close to eyes or brain. {http://www.med.nyu.edu/mininvasive/surgeries/ent/surgery/sinus_nasal.html}
In the past, pituitary tumours were removed using approaches either through the nose or by making large incisions under the lip and connecting it into the nose. These older approaches have the side effect of causing a cosmetic change and the scarring that develops under the lip may cause difficulties with eating and other problems. Instead, a thin flexible endoscope can be placed through the nose to open the sphenoid sinus. A computer is used to track the location of the instruments and to give the surgical team an extra margin of safety in locating and opening the sphenoid sinus. Instruments are used through both nostrils and the tumour is removed under the magnified view of the endoscope. The minimally invasive surgery generally takes 1-2 hours, versus 3-4 hours with the older approaches. The patient generally has much less pain and discomfort. Most patients can go home in a couple of days. {http://www.upsb.org/xq/asp/item.67/qx/html_community/news_view.htm}

A number of MIS procedures will benefit from flexible endoscopes that are extremely thin yet produce high quality images, for example as babyscopes, extending the range of current flexible endoscopes and bronchoscopes. Furthermore, it is important to improve handling and reprocessing abilities. Modular, multi-application devices (one scope for urological, GE, gynaecological, ENT and vascular surgery, etc.) could also present considerable advantages. Technology is currently being developed to make such features possible. Examples of recent developments are the Scanning Fiber Endoscope {Seibel EJ, 2006}, chip-on-the-tip technology {http://www.owi-online.de/} and the PolyScope® , a sterile, disposable flexible endoscope {http://www.matricsmedical.com/PRODUCTS/index_appl.html}.

A.3.2 Hand assisted MIS

The major drawbacks of laparoscopic surgery are two-dimensional view, lack of depth perception and loss of tactile sensation. This has led to the innovation of hand-assisted laparoscopic surgery (HALS). HALS involves the insertion of a surgeon's hand inside the abdominal cavity via a port that is place in an incision of about 7 cm. The position of the handport depends on various factors such as surgeon's dexterity, comfort and target area. The port is capable of maintaining the pneumoperitoneum, necessary for the laparoscopic part of the procedure. Hand-assisted laparoscopic surgery allows tactile sensation and depth perception which may simplify the complex procedures and could also result in reduction of operating time. Hand assistance is an initial tool for the trainee laparoscopic surgeon as it appears to shorten the learning curve associated with laparoscopic procedures. Alternatively, it can be a last resort for the experienced laparoscopic surgeon to bridge the gap between open and completely endoscopic procedures. The main drawback of HALS is that it requires an additional incision, thus increasing trauma. Furthermore, the hand takes up space inside the abdomen and may hamper certain manoeuvres, and may also induce hand fatigue in prolonged procedures. {Gupta P, 2005}

A.3.3 Imaging technology and augmented reality

Minimally invasive surgical visualization currently is in a process of open-ended transformation. When video was first applied to endoscopy, the imaging performance was so poor it was believed that the only way to make it more useful was to make it more realistic, more like what one would see by looking directly at the tissue in question. But in the course of using electronic imaging and computer technology to make these improvements, clinicians came to learn that there is a great deal of additional, and often nonvisible, information that they can bring to bear on an understanding of what is going on in the surgical site. The collective work among physicians and engineers currently aims to reduce the deficiencies of realistic images, identify valuable hyperrealistic techniques, and synthesize and render this information in an intuitive and comprehensible way.

One example is the use of the fluorescent marker 5-ALA, which is taken up preferentially in cancer tissue. Because the marker is concentrated in the diseased tissue only, it allows for easy identification of boundaries between diseased and healthy tissue. In many cases, this technique can be used without a fluorescent marker. The natural autofluorescence inherent in all living tissue can be used to obtain enhanced visual information. Another method of hyperrealistic imaging involves modifying an image in a way that accents certain characteristics, that might not have been visible, through the application of signal processing algorithms.

Both realistic and hyperrealistic images contain important information that can enhance the effectiveness at performing minimally invasive surgery. There still remains the problem of displaying both types in a way that minimizes the confusion that often attends the simultaneous display of disparate information, and that maximizes the meaning of this information to the surgeon. {Chatenever D, 2006}

The concept of augmented reality rose from the desire to optimally exploit virtual data coming from simulations. Its application to the medical world is highly complex and mainly limited to regions where there are many set bone landmarks (neurosurgery, orthopaedics). The aim is to visualize anatomical or pathological structures that cannot be seen directly, by superimposing 3D virtual models on the real patient view. This will allow the surgeon to know the exact position of each structure of the patient, enabling him to prepare well for the operation and even practice the operation in a virtual environment. An example is the ODYSSEUS project (Oncological Disease Identification and Shared Simulation for an

Efficient United Surgical Treatment), which consists of developing tools for an improved diagnosis, preparation, training and realization of the surgical gesture, either alone or within a network. ODYSSEUS will therefore exploit various technologies: telecommunications, virtual reality and surgical robotics. From a CT-scan or MRI, software will provide a 3D copy of the patient on which medical experts will prepare their surgery with the help of a highly realistic simulator. This way, they can learn or rehearse the gesture without risks for the patient. {http://www.ircad.fr/virtual_reality/odysseus.php?lng=en }

A.3.4 Robotics

Robot assisted surgery has the potential to impact the practice of MIS in three important ways:
- Make existing MIS operations easier: routine procedures can be performed more quickly and easily with the increased dexterity and control provided by robotic assistance.
- Make difficult MIS operations routine: Some procedures have been adapted for port-based techniques but are extremely difficult. With the availability of robotic assistance, more surgeons at more institutions will be able to perform these procedures.
- Make new MIS procedures possible: Procedures that are currently not feasible may eventually be performed through small incisions with the help of robotic technology.

Potential tasks facilitated by computers and robotics include information gathering and networking, navigation and guidance, dexterity enhancement, and simulation of virtual environments. The ultimate goal is to create a completely integrated system that converts information from e.g. computed tomography, magnetic resonance imaging, and ultrasonography to action either on a microscale basis or on areas of the body difficult to access. Current applications of robotics include surgical assistance, dexterity enhancement, systems networking and image-guided therapy.

Dexterity is enhanced by placing a microprocessor between the surgeon's hand and the tip of the surgical instrument. This could help to deal with the limitation of performance of a task in a confined space with a restricted range of motion of instruments. Furthermore, motion scaling, in which gross hand movements can be reduced and in which precision and eventually force feedback can be enhanced, allows surgeons to perform tasks not possible today. One such example is retinal vein cannulation with a needle for administration of a local therapy for retinal vein thrombosis involving cannulation of a 100-micron structure. Another future possibility is virtual immobilization or motion stillness, which should eventually allow beating heart surgery under the illusion of stillness by timing the instrumentation and scope with the heart beat.

Potential use of nonvisual imaging techniques, including 3-dimensional modeling and reconstruction of imaging data from CT-, ultrasound- or MRI-imaging, could provide real-time data acquisition of pathological characteristics and monitoring of the delivery of therapy. Other possible roles for computer and robotic assistance in surgery include voice control over surgical manipulators and information manipulators. At present, technology exists to give the surgeon voice control over virtually all operating room equipment including electrocautery, operating table position, endoscopic manipulation, lighting, and telephone.

Currently used robot systems consist of two primary components: the surgeon's viewing and control console and the surgical arm unit that positions and manoeuvres detachable surgical instruments. These pencil-sized instruments with tiny, computer-enhanced mechanical wrists offer more freedom of movement than normal MIS instruments. They are designed to provide the dexterity of the surgeon's forearm and wrist at the operative site through entry ports less than 1 cm (see Figure A.7). This enables the surgeon to enter the chest through keyhole
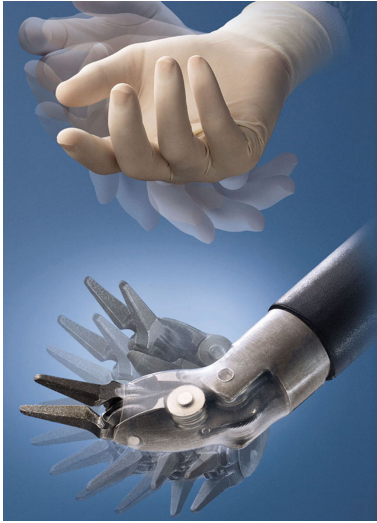
incisions and perform closed chest heart and lung surgery. One port allows access for the endoscope, the other two ports provide access for surgical tools. Instead of the surgeon holding the tools, the robots wrists do, bending back and forth, side to side, and rotating in a full circle, thereby providing greater range of motion than humanly possible. The wrists of the robot mimics the motions made by the physician, who sits at a console outside the operating room. The surgeon peers through an eyepiece that provides high-definition, full-color, magnified, 3-D images of the surgical site provided by the endoscope. The physician moves his hands, which are attached to manipulation controls and the robot follows along.

Figure A.7: EndoWrist® instrument

Unlike current laparoscopic instruments that do not bend, those connected to the robotic arm are designed to mimic the movement of the surgeon's hand and wrist. With this articulation, scaling of the motion, and absence of surgeon tremor, very fine movements can be made in small areas not accessible previously with laparoscopy or thoracoscopy.

In order to make optimal use of robotics, improvements have to be made on the technology itself, the codification of the surgical procedures and the social organization around this new technology. The following improvements can be anticipated: reduction of the size of the trocars from 8 mm to 5 mm, reduction of the bulk of the robot which so far takes a large place in the operating theatre, return of tactile sensation, and addition of an articulation inside the abdomen in order to resolve the problem of crowding at the robot arms. One can imagine a tool looking like a 'Swiss knife' at the tip of an instrument which would avoid continuous tool changes and which would offer more autonomy for the surgeon. This will enable him/her to control him/herself the suction and to tackle a surgical bleeding. Once the problem of 'arms crowding' solved, one can consider an additional articulating arm controlled by the surgeon at the console. The standardized codification of the procedures has to be reinvented.

Trocars placement must take into account the volume of the articulating arm and the presence of an articulation inside the abdomen.

Optimal use of this new technology implies a new social organization. There is now need for a new assistant dedicated exclusively to the well functioning of the robot during the procedure. We could call this person a clinical technician.

Figure A.8: DaVinci® Surgical System

This person needs a clinical as well as a technical background. His/her competence is the determinant factor in operative time and safety of the procedure. The surgeon has to accept the consequences of performing the procedure at distance of the patient and must rely more on technology. These challenges have to be resolved in order for robotics to be more

beneficial in a greater range of laparoscopic procedures and to be introduced in our everyday general surgical practice. The most widespread system today is the DaVinci system (see Figure A.8). {http://www.lap-surgery.com/en/research_ind.htm}

A.4 Ergonomics

The laparoscopic operating room should provide an optimal ergonomic environment and be free of unnecessary safety hazards. In addition to the needs of the surgeons, nursing staff requirements must be considered as well. The movement of heavy, unstable equipment should be eliminated and the presence of floor hazards, such as equipment cords, minimized. Unfortunately, most operating rooms designed primarily for open surgery do not facilitate this. Furthermore, because of the limited vertical motion available on many operating tables, the patient is often positioned too high for the surgeon's comfort. The surgeon is faced with the option of remaining on the floor with the arms uncomfortably elevated or standing—often precariously—on one or more stools. It is therefore advisable that any new OR be designed in a modular fashion so that new equipment can be integrated easily as it becomes available. In designing the OR of the future, the use of robotic surgical assistants may also need to be considered seriously. The design process requires a multidisciplinary approach in order to address the needs of gynaecologists, urologists, neurosurgeons, orthopaedic surgeons, and thoracic surgeons in addition to general surgeons. The OR must be flexible in terms of positioning the patient prone or supine, with legs together or apart, with significant amounts of longitudinal or transverse tilt. Although the wide array of tools required for MIS must be immediately available, they should neither clutter the operating space nor overwhelm the staff during setup and use. It is imperative to remember that the purpose of advanced technology is to facilitate surgery, not to complicate it. {Herron, 2001}

A.5 Education and training

The major disadvantage of MIS is the 'learning curve' of the new techniques. Complications usually occur early in the surgeon's overall experience with minimal access techniques, or when an experienced surgeon is expanding into new procedures. Using fundoplication (surgical treatment of gastroesophageal reflux) as an example, one study specified the first 20 procedures as the period of maximum risk. Recognition of this fact has led to a proliferation of training courses, simulators, web based videos, and mentoring systems. Dr. Marescaus has postulated that the increased morbidity during the learning period of the surgeon can be avoided by means of patient based simulations. He explained that modern imaging techniques enable the creation of a virtual patient on which the surgeon can train the procedure until it can be performed flawlessly. The images of the virtual patient and the recordings of the virtual operation may also be helpful during the actual operation {de Volkskrant, 2005}.

Surgical simulators are now being offered to hospitals as agents to improve training and reduce cost of education. The goal is to train non-experts in the skills needed to deal with specific characteristics of endoscopic surgery, such as the fulcrum effect, the use of long instruments, hampered depth perception, scaling of instruments and misorientation. Computer based simulators will increasingly be more eligible as a training aid, especially due to their extensive assortment of educational features such as video databases, 3D-anatomical atlas, multimedia presentations and video conferences from 'live' procedures. Furthermore, a database that includes recordings from the training sessions provides valuable statistical information on a per user basis. Training with computer-based simulators is a novel approach

with versatile pedagogic potentials that might motivate physicians to improve their skills and better assess new techniques. New medical technologies also demand innovation in design of new instruments and visualization systems. By the introduction of virtual instrument models with a simulator, important feedback may be provided from users during the development phase. The clinical diversity experienced in real life due to differences in anatomy, different pathological processes and stages, requires a large and flexible model basis that is only possible with a computer-based simulator. Individual digital mentors can serve as an integrated part of the simulator. The (virtual) individual mentor can, besides providing relevant training scenarios, also report progress and comparative information. {Herron, 2001}{Verdaasdonk, 2006}

Examples of simulator systems for training of MIS techniques are the Simendo {Verdaasdonk, 2006}, the family of Mentor™ simulators for different surgical specialties {http://www.simbionix.com/Company.html} and the Horus Medical Ultrasonography simulator {http://www.ircad.fr/virtual_reality/horus.php?lng=en}.
A study by Ayodeji determined the expert and referent face validity of LAP Mentor, the first

procedural virtual-reality (VR) trainer. After a hands-on introduction to the simulator a questionnaire was administered to 49 participants (21 expert laparoscopists and 28 novices). There was a consensus on LAP Mentor being a valid training model for basic skills training and the procedural training of laparoscopic cholecystectomies. As 88% of respondents saw training on this simulator as effective and 96% experienced this training as fun it could be accepted in future surgical curricula by both experts and trainees. Further validation of the system is required to determine whether its performance concurs with these favourable expectations. {Ayodeji ID}

Figure A.9: Example of a simulator system of training of MIS techniques

A.6 Risk benefit evaluation

Minimal access surgery has a great impact on patient care. The associated benefits and/or advantages drive fast adoption. This might lead to the adoption of new minimally invasive techniques, while the equality (in terms of clinical outcome) with standard classic techniques has not been established yet. Moreover, the risks and/or disadvantages of minimally invasive procedures may be overlooked.

There are three general advantages of minimally invasive surgery (MIS).
- avoiding large wounds should lead to less postoperative pain; this should in turn minimise the morbidity due to immobility such as postoperative atelectasis, adhesions and venous thrombosis.
- avoiding a large wound should lead to earlier hospital discharge, shorter convalescence and earlier return to work.
- the small portholes of laparoscopic surgery lead to improved cosmesis.

With the exception of cosmesis, which paradoxically is frequently the most important advantage in patient's perceptions, these are usually the indices by which MIS is compared to open surgery. Although it may seem obvious that smaller incisions should result in less pain and quicker recovery, the advantages of minimally invasive techniques can be surprisingly difficult to demonstrate, even in well designed trials.

There are a number of other possible advantages claimed for MIS, such as better visualisation of inaccessible areas, minimisation of risk of adhesive intestinal obstruction, a lower incidence of wound infections and a decreased inflammatory response.

As discussed in paragraph A.5, the major disadvantage of MIS is the 'learning curve' of the new techniques. Because of specific technical problems with MIS techniques, like the lack of normal stereoscopic vision (2D instead of 3D view) giving reduced depth perception, inversion of the direction of movements of the hand and the tip of the instrument (the Fulcrum effect) and reduced tactile feedback, these techniques are more difficult to master than the standard techniques. Complications usually occur early in the surgeon's overall experience with minimal access techniques, or when an experienced surgeon is expanding into new procedures. Proper risk management requires that specific education and training takes place for both new surgeons and new techniques.

Also the use of surgical robots carry a number of disadvantages and risks and should not be applied for any intervention they can technically be used for without a thorough evaluation. Although it may be beneficial for surgeons and hospital management to advertise with the latest technology, patient safety should not be compromised at any time. The best indications still have to be defined and the risk-benefit ratio must be evaluated by independent, non-sponsored studies. For example, the early adoption of a surgical robot system recently lead to adverse events in Germany. The Robodoc system was an orthopeadic surgery robotic tool that promised to be capable of accurately milling the femur for cementless positioning of a hip prosthesis. However, as a side effect of the procedure, a large number of patients received permanent damage to the mucles and nerves resulting is loss of function and permanent pain. One solicitor is filling lawsuits on behalf of 174 German patients.

In addition, the following risks can be identified:
- MIS becomes a high tech venture, involving lots of electronic equipment, cameras, monitors and cables. All this equipment should not hinder the movements of the people working in the operating room, nor compromise their safety. The design of the operating theater needs to be improved to guarantee this.
- Surgeons could become very dependent on novel high tech equipment. They should always bear in mind that the technology may fail and be able to convert to an open procedure.
- Procedure specific risks created by the use of MIS techniques such as port site metastasis following laparoscopic cancer surgery, and port site hernia and haemorrhage following any other type of MIS surgery.
- Multiple access ports increase the risk of iatrogenic injury and excessive instrument traffic could cause an increased rate of infection.
- The creation of a gas filled cavity carries risks. Inadvertent perforation of underlying organs during the initial puncture, haemodynamic and ventilatory changes, and gas embolus are all recognised.
- The design of medical devices that are used for MIS complicates the reprocessing, especially the cleaning. The manufacturers should design the instruments in a way that facilitates reprocessing. The current use of flexible endoscopes within the endogastric track or the upper bronchus asks for the disinfection of the endoscope after use, not

sterilisation. Transgastric surgery, however, presents a greater risk and asks for sterilisation. Flexible endoscopes are not designed for routine sterilisation, however, many hospitals do not have a suitable low temperature sterilisation method available.
- Minimal access procedures usually take longer than conventional open surgery, with consequent reduced throughput; the implications of this may be unwelcome to those responsible for management of healthcare systems. This may, however, be offset by reduced costs from earlier hospital discharge. {B Jaffray, 2005}

In conclusion, each MIS treatment must be evaluated relative to existing alternatives on the evidence of the patient's benefit, surgical morbidity, general and procedure specific risks, short- and long-term outcome including complication rates and cost effectiveness. Only if this is carried out in a responsible way, and if sufficient education and training is provided to the users, then MIS procedures can be applied safely and to the advantage of the patient. Patient safety cannot be compromised just for the sake of a smaller incision.

A.7 References

Beger HG. Progress in gastrointestinal tract surgery: the impact of gastrointestinal endoscopy. Surg Endosc (2003) 17: 342-350.

Calsson LV. Minimally invasise surgery vs conventional exposure using the Miller-Galante unicompartmental knee arthroplasty: A randomized radiostereometric study. J Arthropl. 2006; vol 21:2 151-156.

Chatenever D. Minimally invasive surgical visualization: experience in transition. Surg Endosc (2006) 20: S412-S418.

Dalury DF. Minimally invasive total-knee replacement. Current opinion in orthopaedics 2006; vol 17:1 43-46.

Gupta P. Hand-assisted laparoscopic surgery using Gelport. J Min Acc Surg. 2005;110-115.

Herron DM. The minimally invasibve surgical suite enters the 21st century. Surg Endosc (2001) 15: 415-422.

Jaffray B. Minimally invasive surgery. Arch. Dis. Child. 2005:90:537-542.

Mack MJ. Minimally invasive and robotic surgery. JAMA 2001;285:568-572.

Mack MJ. Minimally invasive cardiac surgery. Surg Endosc (2006) 20: S488-S492.

Ponsky JL. Endoluminal surgery: past, present and future. Surg Endosc (2006) 20: S500-S502.

Tauch C. Minimal invasive surgery in surgical oncology. Eur Sur – Acta Chirurgica Austriaca 2006; vol 38 9-14.

Seibel EJ. A full-color scanning fiber endoscope. Optical fibetrs and sensors for medical diagnosis and treatment applications, Ed. I. Gannot, Proc. SPIE vol. 6083.

Swanstrom LL, et al. Development of a new access device for transgastric surgery. J Gastrointest Surg 2005;9:1129-1137.

Verdaasdonk E. Validation of a new basic virtual reality simulator for training of basic endoscopic skills. Surg Endosc (2006)20: 511-518.

Volkskrant. Ik droom van een robotchirurg. de Volkrant 8 oktober 2005 pag. K07.

Appendix B: Closed loop feedback systems

B.1 Definition

Closed-loop feedback systems are systems that use mathematical algorithms to convert measurement results into outputs like administering medication. An important emerging medical application of closed loop systems can be found in the field of diabetes treatment. Closed-loop systems may also be used in anaesthesia and in muscle and neural stimulation or relaxation (including pacemakers, intracardiac devices and devices for epilepsy prevention). In medical settings these systems lead to circumvention of the need for patient action/compliance and/or professional interference.

B.2 Overview

B.2.1 Diabetes treatment

Diabetes patients using insulin have to take fingertip blood samples several times a day, followed by the determination of the blood glucose level and the subcutaneous injection of insulin. The goal is to keep the blood glucose concentration within the physiological range (6-7 mmol/l), thus preventing the long term problems associated with hyperglycemia and the short term risks of hypoglycemia. For over 40 years now studies are performed on the development of a closed-loop glucose measurement and insulin delivery system, "an artificial pancreas". An ambulatory automated insulin delivery system is a dream for many diabetes patients from the viewpoint of being released from daily blood pricking and insulin injecting. From the medical point of view, benefit can be found in the fact that tight glycemic control reduces and delays serious secondary complications [1-3]. Also the short time risk of hypoglycemia could be decreased by a continuous controlling system. In recent years substantial progress has been made in the development of insulin pumps, algorithms, and sensors bringing closed-loop systems nearer to the market
A closed-loop system for insulin administration consists of a continuous glucose monitoring device, an algorithm-based dose controller and an insulin pump for automated insulin delivery.

Glucose monitoring systems
Since 1999 continuous (or frequent intermittent) glucose monitoring systems enabling retrospective data analysis of blood glucose profiles are commercially available for short time diagnostic use and treatment optimization. Most systems can also be used as an alarm for blood glucose levels exceeding the physiological range.
These systems are minimally or non-invasive and measure glucose concentration in the interstitial fluid of subcutaneous tissue. Main approaches for sampling are:
-    subcutaneous insertion of an electrochemical sensor,
-    subcutaneous insertion of a microdialysis catheter which is perfused with dialysate in which the glucose concentration is measured electrochemically outside the body,
-    transdermal extraction of interstitial fluid in which the glucose concentration is measured electrochemically.

Measurements are mostly based on the generation of hydrogen peroxide from glucose via the enzyme glucose oxidase, which is specific for glucose. The electric current generated due to the oxidation of hydrogen peroxide is measured. Regular calibration using finger sticks and common glucose meters is however still necessary. Most subcutaneous sensors are disposable and last for three to four days. The sensor is connected to a non disposable monitor. Data on glucose levels, insulin dosing, errors and alarms are stored and can be downloaded afterwards.

For glucose monitoring systems precision, accuracy, sensitivity and stability are important, as well as calibration requirements, availability of results, longevity and robustness [1, 4]. Clark error grid analysis is a technique often used to compare the accuracy of sensor readings with the accuracy of standard glucometer readings [1, 5]. Continuous measurement of the glucose level is not compulsory, measuring every 10-15 minutes seems to be sufficient [1]. A number of glucose monitoring systems is already on the market, see textbox B.1.

Textbox B.1: Glucose monitoring systems on the market [41, 42]

- CGMS (Continuous Glucose Measurement System) Gold™ of Medtronic Minimed, Inc.: mainly for short time use, in combination with standard glucometer readings. A subcutaneous sensor for 24-72 hour use sends an electric signal to the monitor every ten seconds. The monitor averages the measured values every five minutes and stores these mean values together with information added by the patient. Data are afterwards downloadable by medical professionals for optimizing therapy.
- Guardian® RT Continuous Glucose Measurement System of Medtronic Minimed, Inc.: patient owned, for long-term use. A radio frequency transmitter sends real-time glucose values from the sensor to the monitor every five minutes. Includes alarms (sound or vibration). Eight hours of glucose values can be viewed by the patient on the screen of a computer for evaluation of food, exercise and lifestyle. A minimum of two finger stick measurements are necessary to calibrate the system every 24 hours. Finger sticks are also required prior to insulin delivery decisions. The sensor is worn for up to three days. After controlled market release in U.S. and FDA approval in August 2005 distribution was expanded in 2005. A recent modification of this system is the Guardian Real-Time monitor (FDA-approval April 2006), that will communicate with Minimed Paradigm 522/722 pumps.
- STS™ of Dexcom is a device with a subcutaneous wire like sensor that wirelessly transmits real-time glucose readings to a hand-held receiver. The sensor must be replaced every three days. It gives high and low glucose concentration alerts and low glucose alarm. DexCom's STS™ was FDA approved on March 27, 2006.
- GlucoDay® of Menarini Diagnostics: a micro pump and a biosensor coupled with a micro dialysis system and worn in a portable pouch around the patient's waist. It needs one point calibration per 48 hour monitoring, two points are recommended for real-time monitoring. Results can be shown on the display and/or transmitted to a computer. The instrument has an alarm function (buzzer or vibration) for hypo- and hyperglycemia. The GlucoDay® is meant for clinical or diagnostic investigations and for analysis of measurement results by a health care team and optimizing the insulin regimen. (CE-marked, Class IIA).
- GlucoWatch® G2® Biographer of Johnson & Johnson/Animas: a noninvasive "wristwatch" sensor collecting glucose from interstitial fluid by reversed iontophoresis, received FDA approval in 2001. In gel collection discs glucose reacts catalyzed by glucose oxidase. The lifetime of the discs is up to 13 hours. Glucose readings are provided every ten minutes but values of two 10-minutes periods are averaged. It includes an alarm function (sound). The sensor is indicated for detection and assessment of hypoglycemia and hyperglycemia episodes, facilitating therapy adjustments. It received FDA approval but is not meant to replace a regular blood glucose meter.

Sontra is developing a continuous non-invasive glucose monitoring system, the Symphony™ Diabetes Management system, together with Bayer Diagnostics. Glucose diffuses through ultrasonically permeated skin. It is analyzed in a biosensor patch with RF transmitter and a glucose meter. Sontra expects to start FDA clinical studies in 2006 in ICU patients. In parallel a home use product is developed.

SpectRX, Inc. is developing the Alte MicroPor™ Laser which creates microscopic pores for the interstitial fluid to cross the outer skin barrier. Glucose can subsequently be measured in an external patch containing a glucose sensor. At the moment clinical investigations for this monitor are being performed [6].

The FreeStyleNavigator™ of Abbott Diabetes Care/Therasense is currently under review for FDA approval. It consists of a sensor placed just under the skin for several days with a plastic sensor mount adhered to the skin like a patch. The second part is a wireless (RF) transmitter

and the third part a small receiver designed to display glucose values and trends, with data storage and alarm function

GluMetrics is developing glucose sensors based on fluorescence: the GluGlow™ technique. GluGlow is a boronic acid-based polymeric material, which glows in the presence of glucose. Their first device, GluCath™, is due to be released in mid 2007, and is intended to be used for continuously monitoring of hospitalized patients. It is a catheter device that uses a thin fiber-optic cable incorporating GluGlow. A next development, BetaGlow™ will comprise the sensing component of a closed-loop system.

Several other sensors are being developed that can be implanted for a longer or shorter term. Medtronic Minimed, Synthetic Blood International and Dexcom have done researches in this field. The DexCom™ LTS system is implanted under the skin in the abdomen and is designed to function for up to one year, after which it must be replaced by a physician. Readings are transmitted wirelessly to a hand-held receiver. The system is under clinical investigation and is not yet available on the market [4, 6].

Other techniques based on the use of ultrasound (to increase permeability and transdermal transport), fluorescence, near or middle infrared light (to measure glucose on the base of absorption, reflection or optical rotation), or "smart" glucose sensitive gels (that show reversible viscosity change under influence of glucose leading to controlled release of insulin [3, 6]) are not ready for marketing.

Blood glucose monitoring systems must meet the European standard EN-ISO-15197: 2003 In vitro diagnostic test systems – Requirements for blood-glucose monitoring systems for self-testing in managing diabetes mellitus.

Algorithm-based dose controllers

As a next step to build a closed loop system, an automated feedback system is necessary that translates blood sugar level (BSL) readings into appropriate insulin dosage. The system must be based on a validated algorithm. This algorithm should mimic the response of the pancreatic ß-cell on glucose levels, which includes e.g. "first phase insulin release", "second phase insulin release", the so called "glucose priming" effect, and ß-cell inhibition in proportion to plasma insulin level [2]. There are two main categories of control algorithms used for insulin closed loop systems: "proportional-integral-derivative" (PID) controllers and "model predictive control" (MPC) [2, 8, 9].

Mimicking the ß-cell response shows some complications:
- the system must be able to imitate the insulin-secretion profile for meal (BSL increasing) and exercise (BSL decreasing),
- depending on the type of sensor and its location, different delays and noise will be present,
- glucose monitoring is accompanied by a delay due to glucose diffusion and measurement (sensing delay). Thus, glucose measurements are not completely "real-time" [1, 2, 10]. This is a problem in case of large disturbances such as those following daily meals. Similarly, depending on the type of pump and its location (subcutaneous or intraperitoneal), the insulin dynamics will be different [2]. They give a delay in the peak of the glucose lowering effect due to the time necessary for absorption of insulin from the subcutaneous or intraperitoneal environment (insulin delay) and for insulin action.

The delays must be dealt with by algorithms. Noise can be reduced by the use of filters in the algorithm [2, 7].

There are some other factors to be dealt with using algorithms for closed-loop systems:
- the insulin sensitivity of an individual may vary substantially, e.g. due to changes in fitness or health, time of day or mental stress levels,

- insulin absorption characteristics and sensor dynamics can vary due to a new placement of the delivery catheter or sensor [9],
- the performance of algorithms can be affected by factors like dietary fat (delays gastric emptying and induces postprandial insulin resistance), alcohol (suppresses hepatic glucose production), and caffeine (induces insulin resistance) [10].

An interface allowing information input about these factors into the pump controller by the patient could add to the precision of the system, but makes the system less "closed" [10]. Medtronic Minimed, Inc. is developing a semi-automated system using an advanced mathematical algorithm applied to a "smart" insulin pump that integrates real-time continuous glucose monitoring. The system proactively suggests insulin dosages to the patient. The recommended dose must be confirmed before insulin is delivered. Another point is that also information about the functioning (or non-functioning) of the insulin pump should reach the controller [9]. Research on the further refinement of control algorithms for an artificial pancreas is still continuing [11].

Smart insulin pumps
External pumps can be used for Continuous Subcutaneous Insulin Infusion (CSII). The first commercially available insulin pumps for subcutaneous administration and ambulatory use appeared on the market around 1980 [2]. For examples of newer pumps, see Textbox B.2. Short acting insulin analogues are administered at a low rate. The insulin reservoir has to be filled by the patient every two or three days. Currently, pumps with memory allow for data downloading. An external pump delivering a rapid analogue of insulin is considered "the gold standard of insulin delivery".

Textbox B.2: Some of the newer external insulin pumps on the market [7, 12]

- Paradigm® 512 and 712 of Medtronic Minimed, Inc.: the Paradigm Link® Blood Glucose monitor automatically transfers blood glucose results (obtained with test strips) to this pump through RF transmission. The pump's calculator recommends an insulin dose and, subsequently, the patient can simply push a button to administer the recommended dose or can select to change the dose. The patient has to administer boluses before meals and infusion rate can be manually adjusted before physical exertion etc. A Bolus Wizard® calculator gives insulin dosing recommendations. Not yet in Europe: Paradigm® 515 and 715l; Paradigm® 522 and 722.
  Medtronic Minimed, Inc. expects for their next generation systems the integration of a "smart" insulin pump with real-time continuous glucose monitoring (like the Guardian Real Time), so patients will have access to real-time glucose data directly from the pump an the pump would calculate a recommended dose.
- Deltec Cozmo of Smiths Medical MD: can be combined with the CoZmonitor blood glucose monitor, which can be attached to the back of the Deltec Cozmo® insulin pump to create an all-in-one device. The pump keypad and screen are used glucose testing functions and results. The meter reads blood sugars directly into the pump via an infrared port, and can be used during plane flights. Bolus recommendations are given after entering carbohydrates in the meal and/or blood sugar levels.
- OmniPod™ Insulin Management System of Insulet Corporation: a two-part system of a FreeStyle® blood glucose monitoring technology and a device for continuous subcutaneous insulin delivery with automated canula insertion. It is worn on the skin like an infusion set and delivers insulin according to pre-programmed instructions transmitted wirelessly from the Personal Diabetes Manager (PDM), a hand-held device. The OmniPod monitors the operation and checks blood glucose levels using FreeStyle blood glucose test strips. It includes a suggested bolus calculator. The system received FDA 510(k) clearance in 2005.
- Animas IR-1250 of Animas (FDA approved but not yet available in Europe): the glucose meter interface ezManager Plus™ enables downloading of data from pump and glucose meter to a computer. There is not yet a direct input from blood glucose meter to pump. Animas is expecting to utilize a direct infrared (IR) port for blood glucose data transfer. Animas is developing an external micropump for subcutaneous injection of insulin which can be directly taped on the skin and is operated and programmed through a Remote Control Device.
- Accu-Chek Spirit of Roche (formerly Disetronic): to be used with Accu-Chek® Pocket Compass software with bolus calculator on a palmOne™ device and Accu-Chek® blood glucose meter. Received FDA clearance in 2005 and is now on the European market.

The intraperitoneal insulin administration by implantable pumps gives a more physiological insulin delivery. Implanting pumps is, however, more expensive and experience with implantable pumps is limited. In 1999 approximately 1000 pumps were implanted [1]. Pump

pocket infections, catheter blockage and device failure may necessitate surgical removal. Stability of insulin is a point of attention.

There is only one implantable insulin pump approved and commercialized in the EU (Minimed Medtronic 2007, CE mark). This pump is implanted in the lower left quadrant of the abdomen and a 20-30 cm long catheter is placed such that the tip is in the intraperitoneal cavity. U400-regular insulin is filled across the skin into a pump reservoir every two to three months. Insulin delivery is modulated by the patient using an external programmer using RF telemetry, according to the results of self blood glucose monitoring. Bolus doses before meals can be given by pushing a button. The programmer must be synchronized with only one pump, assuring other implantable devices are not affected. The life span of the pump battery is dependent of the daily insulin delivery, but is suggested to be at least seven years. Implantable pumps offer advantages for patients who have difficulty in maintaining consistent glycemic control, even using CSII [13].

Insulin pumps must meet the European standard EN 60601-2-24:1998 Medical equipment – Part 2-24: Particular requirements for the safety of infusion pumps and controllers.

Closed-loop systems for insulin administration
Based on the abovementioned components prototypes of closed-loop systems have been developed. The two main approaches are [1]:
-    Extracorporeal: subcutaneous glucose monitoring and subcutaneous insulin administration (s.c.-s.c.). This system is a minimally invasive solution that can benefit from the experience of more than 200,000 external insulin pump users. Therefore it seems to be the best possibility for widespread application.
-    Implantable: intravenous glucose monitoring and intraperitoneal insulin delivery (i.v.-i.p.).

Intravenous sensors implanted in the circulatory system, e.g. vena cava, are mainly for short time use in a hospital environment. There is less experience with implantable pumps delivering insulin intraperitoneally [1, 13, 14].

Due to longer delays particularly users of s.c.-s.c. systems will have to enter information on meals or physical exertion, and the loop system is not fully closed anymore. There are different ways to handle mealtime insulin delivery:
-    "fully closed-loop": insulin is administered by evaluating the rise in postprandial glucose.
-    "semi-closed loop" or "closed-loop with meal announcement": patient gives information about time and size of the meal in advance and the controller advises on an insulin bolus.
-    "closed-loop with qualitative meal announcement": patient gives information about time of the meal and the controller switches to a more aggressive mode of insulin delivery.
Meal announcement or "feedforward control" improved results [1, 9, 10].

A remaining restraint on the performance of an artificial pancreas is that it uses only insulin to control blood glucose levels, while the physiological pancreas uses both insulin and glucagon. It is difficult to prevent hypoglycemia without glucagon or glucose as an additional manipulated input [9].

Studies with continuous glucose monitoring systems in closed-loop situations were limited in number of subjects as well as in duration [1], see Textbox B.3.

Although small-scale laboratory studies with closed-loop systems have been performed, performance in routine in the clinic as well as in the home setting has yet to be demonstrated [1].

Textbox B.3: Studies on continuous glucose monitoring in closed-loop systems

- In 2004 an evaluation was published of an external physiological insulin delivery (ePID) algorithm, an adoption of a PID-controller [15]. GCMS/Guardian of MedtronicMiniMed was used as a sensor, calibrated before the start of closed-loop control, and checked regularly. Six subjects received each four meals in 27.5 hr, without meal announcement. Preprandial and postprandial (2hr) glucose levels were 5.8 ± 1.2 and 9.8 ± 1.6 mmol/l (mean ± SD), respectively. Morning glucose level after overnight control was 6.8 ± 1.0 mmol/l.
- Another study published in 2004 used the sensor (under development) SCGM1 of Roche Diagnostics in a s.c.-s.c. closed-loop system with meal announcement [1,16]. An empirical algorithm was used that was converted to a model predictive (MPC) framework. The closed-loop system was evaluated in twelve patients treated with CSII. Control with the algorithm was compared to standard self-directed therapy over study periods of 32 hr. Each period included ingestion of four meals and quantitative meal announcement was given. The algorithm achieved a mean monitored glucose concentration of 6.9 mmol/l vs. 6.2 for self-directed therapy. It reduced the number of hypoglycemia interventions. During algorithm therapy 56% of SCGM1 values were within the 5.0-8.3 mmol/l range compared with 33% with the self-directed therapy.
- In five critically ill patients on an intensive care unit a study was performed in 2003 using GCMS as a sensor, coupled with a proportional integral control algorithm based on a sliding scale approach for automatic intravenous infusion of insulin [5]. In four patients manual intervention was needed due to the real-time sensor reading of blood sugar levels deviating more than 20% from the glucometer value. The conclusion of this study was that more work was needed for the refinement of the algorithm and the improvement of real-time sensor accuracy, and that the algorithm was not yet suitable for use in ambulatory patients.
- In 2004 a study was published on the testing of an i.v.-i.p. closed-loop system in four diabetes patients over 48 hr. A long-term sensor system (LTSS) was used, containing a sensor of MedtronicMiniMed, and was combined with a implantable physiological insulin delivery system (iPID). Quantitative information on breakfast, lunch and dinner were given. During the first 24 hr empirical tuning of the algorithm took place. During the second 24 hr control period 4% and 7% of the time was spent below 4.4 mmol/l in the postprandial period and outside meal conditions, respectively, 12% and 32% was spent in the region 4.4-6.7 mmol/l, 63% and 60% was spent in the region 6.7-13.3 mmol/l, and 20% and 2% was spent above 13.3 mmol/l [17].

Marketing in the coming years
A personal wearable treatment system is the ultimate goal. Although there are several sensors on the market or at near approval, reliability and accuracy of the presently available monitors is not yet considered sufficient to replace invasive measurements obtained with blood glucose meters for decisions on insulin dosage. Currently, these sensors are promoted to detect trends and track patterns in glucose levels and for an alarm function.
Sensor lifetime is still limited. For long-term use time-related effects such as increasing lag because of progression of biologic fouling or foreign body fibrosis may cause problems on the sensor surface [18]. Besides, implantable intravenous glucose sensing is invasive and may cause biocompatibility problems.
Although miniaturized external pumps as well as an implantable insulin pump are available and reliable nowadays, glucose sensors and algorithms have not yet proved to be reliable enough at the moment for real closed-loop administration of insulin [13]. Nevertheless, several all-in-one devices have been introduced recently to the market or are pending for FDA clearance. They consist of a continuous glucose monitor, a dose advising controller and a smart insulin pump. Finger prick glucose monitoring is still necessary for regular calibration and required for confirmation of glucose levels before insulin doses are programmed. Additionally, the patient has to enter information on meals, exertion etc. Therefore these systems have a semi-closed-loop character, advising patients on dosing . The tremendous research efforts in this field will probably result in continuing innovations in the coming years, coming close to closed-loop systems.
Closed-loop systems for insulin administration may be used first in controlled environments like intensive care units. Systems for short-time use could include an intravascular real-time glucose sensor. For critically ill patients in the surgical intensive care unit and for diabetes patients with acute myocardial infarction tight glucose control significantly decreases mortality [1, 10].
The first generation of closed-loop systems will probably not achieve complete normalization of the glucose profile. When the system can maintain or improve the level of glycosylated

hemoglobin (HbA1c, an indicator of how well the blood glucose has been controlled over the past three months) and reduce the frequency of hypoglycemia it could be suited for the treatment of a small group of well motivated patients. For home treatment the device must be easy to program and to use, the user interface needs to be straightforward, the calibration of the glucose sensor needs to be easy, fault detection must be incorporated, and warnings must be provided [9]. In addition, patient education will be very important to expand the patient population having the necessary advanced skills [10].

The number of diabetes patients world-wide has risen from 30 million in 1985 to 177 million in 2000 and will be at least 300 million in 2025 [19]. Some 40% need insulin injections [20]. Only for a part of the diabetes patients a closed-loop system will be the optimal therapy. On the other hand much research is performed on less encumbering ways of administering insulin, like oral, buccal (Oralin™), transdermal or inhaled (Exubera®, Technosphere®) insulin. Resulting products and advanced transplantation techniques may eventually reduce the need for parenteral insulin administration.

Closed-loop dosing systems could possibly have advantages in the administration of other substances like anticoagulants.

Possible risks

The possible risks of (semi-) closed-loop systems can be clustered around several aspects of these systems.

- Sensor reliability

Inaccurate glucose values or inappropriate alarms could result in inappropriate administration of insulin. Tissue reactions to implanted parts of a sensor can interfere with accuracy and reliability [10]. Therefore lifetime is limited and regular calibration of non- or minimally invasive monitors is still required.

Minimum requirements for properties as reliability and accuracy of sensors have to be determined.

- Invasiveness

Implantation of sensors or pumps requires surgery and brings the risk of infections. Intravenous monitoring may cause thrombosis or embolization [18]. Implanted pumps require surgical removal after their lifetime. Infections, catheter blockage and device failure may necessitate early removal. Regularly a sterile refill procedure has to be performed and the stability of insulin at body temperature is a point of attention. The experience with implantable pumps is limited.

- Algorithms

Blood glucose is complicated by several variables like food intake, physical activity, stress, illness and sleep. Rapid changes in blood glucose are difficult to be dealt with by algorithms without patient input of information. Failure of algorithms may cause substantial risk because people may put a lot of faith in advised or recommended doses.

Good control by an algorithm may bring along the risk of masking technical operating problems [9]. Information about the functioning of the pump should reach the controller.

- Wireless information transfer

Radio frequency (RF) transmission of data may give interference with cell phones or other radio traffic and can give problems inside planes. Interference with other medical devices and with devices of other patients must be made impossible.

European standards in this field have been developed by ETSI (European Telecommunications Standards Institute) for implantable devices. More information on wireless data transmission in medical technology is presented in Appendix E.

- User interface

The user interface must be straightforward and programming and calibration must be easy. The patient must be capable to deal with the information provided by the system and must be well trained. In addition, it should not be possible to push buttons such as for bolus injections inadvertently. Small pumps with small buttons and displays may give ergonomic problems, especially for elderly people or people with a reduced vision.

- Data storage

Battery removal or static electricity may cause loss of stored settings and historical data.

At the moment there are no really-closed-loop systems for diabetics that are ready for marketing. Although the newly developed systems are not yet perfect, these near-closed-loop systems may result in better blood glucose levels than can be reached with five times daily finger pricking and insulin injecting. For each patient a risk-benefit analysis will be important before deciding for a (semi-) closed-loop system. Closing the loop would entirely overcome the necessity of patients to occupy themselves daily with glucose monitoring, insulin dosing and understanding complex information, but it must be very sure that such a system brings no risks of catastrophic failure [7]. Systems not measuring brain glucose and not using glucagon as a second hormone will probably never be "perfect" [1, 7]. At moment there is no widely accepted system to assess specifically the performance of closed-loop systems for insulin delivery, although recently a grading system to assess closed-loop glucose control from the clinical point of view was suggested [1, 21]. Experience with near-closed-loop systems will provide more information for deciding whether and how to close the loop.

B.2.2 Anaesthesia

The monitoring and control of depth of (inhalation or intravenous) anesthesia during surgery is very important. The goal of closed-loop control in anesthesia is reducing the necessity of clinician intervention and of the number of phases of inadequate control. Adjustments can be made more frequently by a computer than by manual control but it cannot anticipate on future events. Additionally it may reduce the consumption of anesthetics.

Computer-controlled closed circuit and closed-loop feedback systems for dosing volatile anesthetic agents, oxygen and water in the inspired gas ("anesthetic work stations"), are well known devices for which standards have been drawn up like the European standard EN ISO 8835 "Inhalational anaesthesia systems" and IEC 60601- 2-13: 2004/A1:2006 Medical electrical equipment – Particular requirements for the safety and essential performance of anaesthetic workstations". Closed circuit brings a decrease in environmental pollution and in costs. For feedback control several variables are used like oxygen saturation, end-tidal carbon dioxide concentration, water content of respiratory gases and end-tidal concentration of volatile anesthetic agents [22]. Examples of these feedback-controlled ventilators for closed system anesthesia are PhysioFlex, Evita and Zeus® (market introduction in EU in 2003) of Dräger Medical AG (Lübeck, Germany) [22, 23].

Target-controlled infusion (TCI) maintaining a preset target concentration of the anesthetic in plasma is based on a pharmacokinetic model of the anesthetic and has been successfully used in open-loop systems, but can also be used in closed-loop control when there is a reliable and consistent signal for feedback utilization. Brain function monitoring may produce such information. Auditory evoked potentials (AEP) or somatosensory evoked potentials (SEP) have been used in studies as a feedback signal for TCI. A clinical study using AEP as the input signal for closed-loop administration of propofol in 60 patients was published in 2003 [24]. Mahfouf et al. developed a closed-loop control scheme with a fuzzy multivariable controller, using AEP values during the maintenance phase of the anesthesia, which could be used for the infusion of an anesthetic and an analgesic drug (propofol and remifentanil)

simultaneously. The controller was tested in simulations; clinical trials in humans were not performed [25].

With anesthetic agents SEP (pertaining to sensations received in the skin and deep tissues) has been shown to give increased latency as anesthetic depth is increased. SEP has a better signal to noise ratio than AEP. A proportional integral (PI) closed-loop control system was developed using SEP as feedback measure. Experiments in rats with propofol as the anesthetic agents had promising results. However, further experiments with animals and experiments with humans have yet to be performed [26].

Target-controlled infusion or inhalation can also be based on a target like the "bispectral index" (BIS™). BIS™ is a nonlinear function of electroencephalogram waveforms and can be used as a measure of the depth of anesthesia. BIS™ values range from 0 to 100, with 100 signifying full awareness and 0 indicating no brain activity. BIS™ is developed by Aspect Medical systems (Newton, MA, USA) and is available in modular form and is licensed for integration in patient monitoring systems of leading manufacturers. A number of studies have been performed to close the loop based on BIS™ measurements, by manipulating the anesthetic delivery rate to maintain BIS™ at a desired set point value [9]. In 2003 a study was published with 20 patients receiving propofol infusion using BIS and a PI-differential control algorithm for feedback regulation. The system was able to provide clinically adequate anesthesia in all patients [27]. In 2004 a study with 23 patients was described who received isoflurane via a vaporizer, with either manual or closed-loop control. To avoid adverse effects of measurements artifacts end-tidal concentrations of isoflurane were measured as a second controlled variable. No human intervention was necessary in the closed-loop control group. In the manual group nine phases of inadequate control were recorded, compared with one in the closed-loop control group. During all phases of the surgery the averages of the performance parameters (mean absolute deviation and median absolute performance error) were more than 30% smaller in the closed-loop control than in manual control. The authors concluded that closed-loop control with BIS™ using isoflurane can safely be applied clinically and performs significantly better than manual control, even in phases of abrupt changes of stimulation that cannot be foreseen by the control system [28].

More recently another monitoring system which is based on EEG signals has become commercially available in Europe: the SNAP II™ sensor (Everest Biomedical Instruments, Inc., MO, USA) [29-32]. This system has not yet been used for closed loop anesthesia.

In a recent advice of the American Society of Anesthesiologists [32] some drawbacks of brain function monitors are mentioned. For instance: the values generated may differ when different combinations of anesthetics are used, which means that a specified value may not correlate with a specific depth of anesthesia. Common events during surgery (e.g. electrocautery, lasers, warming devices) may introduce artifacts into the values derived. Therefore this Society advices not to use brain function monitors routinely for general anesthesia patients.

Marketing in the coming years
At the moment modern closed system ventilators have feedback control for anesthetic delivery based among others on measurement of end-tidal anesthetic concentrations. Guidance based on EEG derived parameters like BIS™ and SNAP™ is relatively new. Closed loop systems based on BIS™ are used only under experimental conditions and have to be tested more extensively under divergent clinical circumstances. There are no commercial closed loop systems based on AEP or SEP that are ready for marketing.

Possible risks
Anesthesia systems being "closed" brings risks like accumulation of foreign gases (e.g. methane) which can be dealt with by flushing the system intermittently, or gas leakage which can be prevented by using gas tight tubes or masks [23].
Automatic dosing of anesthetics based on a closed loop system brings risks because failing performance may endanger patients directly. A direct and uniform correlation of measured parameters with the depth of anesthesia must be determined and interference with other events or devices must be precluded. Monitors of depth-of anesthesia result in an index that is dimensionless, numbering from 0 to 100. However the scales of different types of monitors (e.g. BIS™ and SNAP™) are not interchangeable [31].
The safety of automated closed-loop systems must be proven and the controllers must be tested. In 2004 Struys et al. described a simulation methodology with virtual patients to test controllers. They compared two controllers ('patient individualized model based' and 'proportional integral derivative') for BIS™-guided propofol administration. In the model based system the patient specific relation between propofol concentration at effect site and BIS value was determined during the induction phase and used in the controller during the surgical phase. This controller gave better results than a standard PID controller [33]. Measurement of anesthetic effects may have an advantage over measurement of concentrations of anesthetics because it compensates for inter patient variability in pharmacokinetics, pharmacodynamics and drug sensitivity. However measurement artifacts can have negative effects [28].

B.2.3 Neural and muscular stimulation
Closed loop systems have been designed for clinical trials in some applications in this field.

Epilepsy
The frequency of epileptic seizures can be reduced by stimulating different anatomical targets. This is important for patients that are refractory to antiepileptic medications. For these patients it is frustrating that their activities are limited by their vulnerability to sudden incapacitation, due to the occurrence of seizures. Advances are made in miniaturizing of ambulatory electroencephalography and seizure anticipation technology. This enables the development of closed loop systems which can improve the quality of life of patients with refractory epilepsy [34]. Clinical studies have been performed with external as well as with implantable closed loop stimulation systems. Currently patients are recruited for a clinical phase III study with the Responsive Neurostimulator (RNS™) system of Neuropace, Inc. (Mountainview, CA, USA) [35]. The system is implanted in the head and detects electric activity from the brain that is indicative for epileptiform activities. It responds by sending electrical stimulation to a small part of the brain to stop the seizure ("responsive stimulation"). Diagnostic information is stored and can be downloaded by an external programmer. The efficacy of the system for the treatment of epilepsy has to be determined. The trial is expected to last 2 or 3 years.

Functional electrostimulation
Open loop functional electrical stimulation (FES) systems are in use for rehabilitation training to reach the recovery of lost or impaired capacity for movement, but are also important for balance retraining, bone density and cardio-vascular condition. Electric current pulses (via surface or implantable electrodes) stimulate intact peripheral nerves and produce muscle contractions and thus joint movements in paralyzed individuals. Nowadays closed loop devices are being developed that try to mimic the fine physiological movement control systems for the non-linear neuromuscular-skeletal system. These are meant for e.g. spinal

cord injured patients or hemiplegia patients. For example, systems have been developed for restoration of regular walking of hemiplegia patients after appropriate gait training [36, 37]. Several control systems have been used. Classical algorithms like proportional integrative derivative (PID) controllers showed insufficient performance and more adaptive systems were developed like model based neural controllers (NeuroPID), sliding mode controllers and an adaptive control system (Neuradapt) based on artificial neural networks [37, 38]. Adaptive systems are monitoring muscular condition and fatigue. For more complex stimulation setups more complicated systems have to be developed like multi-input multi-output (MIMO) systems. The ability of neural network to adapt their parameters on-line seems to be important for the control of muscular systems by FES [38].

The development of good closed-loop controllers for FES is difficult. Problems are due to sensor noise, time delays introduced by controllers and time consuming training procedures for neural networks [36].

Muscle relaxation during anesthesia
Experiments with closed loop control of muscle relaxant administration have been performed for nearly twenty years now, using different algorithms and relaxants. A recent publication describes a muscle relaxation monitor (TOf Watch X, Organon, Oss, The Netherlands) connected to a laptop computer running a controller algorithm program that communicated with a syringe pump delivering a rocuronium infusion. This closed loop arrangement was evaluated during anesthesia in 15 patients [38]. Closed loop control of muscle relaxant administration is however not yet daily clinical practice. Problems may be caused by a delayed onset time, non-linearity of the dose response curve and differences between patients in sensitivity to muscle relaxants.

B.3   Conclusion

Closed loop systems are intrinsically characterized by a close cooperation of different devices: a sensor for measurement of diagnostic parameters(s), a controlling algorithm and a therapeutic device. Some of these systems have to deal with very complex physiological processes, which may be critical processes too (like systems for insulin therapy, or anesthesia). It is essential that the system reacts promptly and properly on a diversity of physiological conditions and events. Furthermore, closed loop systems taking over control means that it may take some time before medical professionals or patients detect a deviation in device functioning, or a device action that is deteriorating or fatal for the patients health. Therefore, failing of closed loop systems may have serious consequences for patients. This means that closed loop systems controlling critical physiological processes should have to meet very stringent requirements with regard to performance and reliability before they are placed on the market. Data transfer between the components must be impeccable. Risk assessment and clinical studies should be extensive and take into consideration all possible physiological conditions and environmental circumstances.

Because closed loop systems are complicated devices, some of which generate a considerable lot if data to be analyzed or dealt with, extensive training of medical professionals and/or patients is of essential importance.

At the moment a standard on closed loop systems is being developed: IEC 60601-1-10 Medical electrical equipment - Part 1-10: General requirements for basic safety and essential performance - Collateral Standard: Requirements for the development of physiologic closed-loop controllers. The task of the working group (IEC – SC62A – JWG 5) is: to develop general process requirements and guidance on the application of physiological closed-loop

controllers to medical electrical equipment and medical electrical systems. The circulation of the committee draft for comments closed on 26 May 2006. Completion of this standard is expected in 2007 or 2008.

Abbreviations

AEP	auditory evoked potentials: electric responses of the brainstem, the auditory radiation and the auditory cortex to auditory sound stimuli.
BIS	bispectral index
BSL	blood sugar level
CGMS	continuous glucose monitoring system
CSII	continuous subcutaneous insulin infusion
HbA1c	glycosylated hemoglobin, a measurement used to reflect glucose levels over 8 to12 weeks
LTSS	long-term sensor system
MPC	model predictive control
PI	proportional integral
RF	radio frequency
SEP	somatosensory evoked potentials: electric responses from the spinal cord or cerebral hemisphere to electrical stimulation or physiological activation of peripheral sensory fibers.
STS	short-time sensor
TCI	target-controlled infusion

Manufacturer's websites:

Animas	http://www.animascorp.com/index2.shtml (access date 05-10-06)
Dexcom	http://www.dexcom.com/ (access date 05-10-06)
Insulet Corp.	http://www.myomnipod.com/ (access date 10-10-06)
Medtronic	www.minimed.com (access date 05-10-06)
Menarini Diagnostics	http://www.menarini.com (access date 05-10-06)
Roche	http://www.roche-diagnostics.com/ (access date 05-10-06)
Smiths Medical	http://www.smiths-medical.com/ (access date 10-10-06)
Aspect Medical systems:	http://www.aspectmedical.com/ (access date 07-11-06)
Dräger Medical AG & Co KG:	http://www.draeger-medical.com (access date 07-11-06)
Everest Biomedical Instruments	http://www.everest-co.com/ (access date 07-11 -06)
Neuropace, Inc.:	http://www.neuropace.com (access date 07-11-06)

B.4   References

[1]   R. Hovorka, *Continuous glucose monitoring and closed-loop systems.* Diabet Med *23,* 1-12 (2006).

[2]   G. M. Steil, A. E. Panteleon and K. Rebrin, *Closed-loop insulin delivery-the path to physiological glucose control.* Adv Drug Deliv Rev *56,* 125-144 (2004).

[3]   S. Tanna, M. Joan-Taylor, T. S. Sahota and K. Sawicka, *Glucose-responsive UV polymerised dextran-concanavalin A acrylic derivatised mixtures for closed-loop insulin delivery.* Biomaterials *27,* 1586-1597 (2006).

[4]   C. W. Chia and C. D. Saudek, *Glucose sensors: toward closed loop insulin delivery.* Endocrinol Metab Clin North Am *33,* 175-95,xi (2004).

[5]   F. Chee, T. Fernando and P. V. van Heerden, *Closed-loop glucose control in critically ill patients using continuous glucose monitoring system (CGMS) in real time.* IEEE Trans Inf Technol Biomed *7,* 43-53 (2003).

[6]   Diabetes technology- future monitoring. 2006.
       http://www.diabetesnet.com/diabetes_technology/insulinpumps_future.php

[7]   W. L. Clark, *An artificial pancreas - How close are we to closing the loop?* JDRF
       Countdown magazine, Juvenile Diabetes Research Foundation International 2-8 (2006).

[8]   H. C. Schaller, L. Schaupp, M. Bodenlenz, M. E. Wilinska, L. J. Chassin, P. Wach, T.
       Vering, R. Hovorka and T. R. Pieber, *On-line adaptive algorithm with glucose
       prediction capacity for subcutaneous closed loop control of glucose: evaluation under
       fasting conditions in patients with Type 1 diabetes*. Diabet Med *23,* 90-93 (2006).

[9]   B. W. Bequette, *A critical assessment of algorithms and challenges in the development
       of a closed-loop artificial pancreas*. Diabetes Technol Ther *7,* 28-47 (2005).

[10]   H. A. Wolpert, *A clinician's perspective on some of the challenges in "closing the loop"*.
       Diabetes Technol Ther *5,* 843-846 (2003).

[11]   M. S. Ibbini and M. A. Masadeh, *A fuzzy logic based closed-loop control system for
       blood glucose level regulation in diabetics*. J Med Eng Technol *29,* 64-69 (2005).

[12]   Insulin pumps-today'pumps. 2006.
       http://www.diabetesnet.com/diabetes_technology/insulinpumps.php

[13]   B. Catargi, Current status and future of implantable insulin pumps for the treatment of
       diabetes. Expert Rev Med Devices 1, 181-185 (2004).

[14]   J. Pickup and H. Keen, *Continuous subcutaneous insulin infusion at 25 years: evidence
       base for the expanding use of insulin pump therapy in type 1 diabetes*. Diabetes Care
       25, 593-598 (2002).

[15]   G. M. Steil, K. Rebrin, F. Hariri, Y. Chen, C. Darwin and M. F. Saad, *Continuous
       automated insulin delivery based on subcutaneous glucose sensing and an external
       insulin pump*. Diabetes *53,* A2 (2004).

[16]   P. Galley, R. Wagner, H. Buck, S. Weinert, S. Bousamra, J. Long, A. Thukral, D.
       Kenyon, G. Freckmann, N. Jendrike, C. Haug and A. Abicht, *Use of subcutaneous
       glucose measurements to drive real-time algorithm-directed insulin infusion
       recommendations*. Diabetes Technol Ther *6,* 245-246 (2004).

[17]   E. Renard, A. E. Panteleon, P. Leong, J. Han, M. Kolopp, M. Miller, V. Shahmirian, K.
       Rebrin and G. M. Steil, *Efficacy of closed loop control of blood glucose based on an
       implantable i.v. sensor and intraperitoneal pump*. Diabetes *53,* A114 (2004).

[18]   W. K. Ward, M. D. Wood, H. M. Casey, M. J. Quinn and I. F. Federiuk, *An implantable
       subcutaneous glucose sensor array in ketosis-prone rats: closed loop glycemic control*.
       Artif Organs *29,* 131-143 (2005).

[19]   WHO. WHO-Health topics-Diabetes mellitus-fact sheet 236: The cost of diabetes.
       2002. http://www.who.int/mediacentre/factsheets/fs236/en/

[20]   WHO. WHO-Health topics-Diabetes mellitus-fact sheet 138: Diabetes mellitus. 2002.
       http://www.who.int/mediacentre/factsheets/fs138/en/

[21] L. J. Chassin, M. E. Wilinska and R. Hovorka, Grading system to assess clinical performance of closed-loop glucose control. Diabetes Technol Ther 7, 72-82 (2005).

[22] J. A. Baum, *New and alternative delivery concepts and techniques*. Best Pract Res Clin Anaesthesiol *19,* 415-428 (2005).

[23] P. Schober and S. Loer, *An innovative anaesthesia machine: the closed system.* Current opinion in aneasthesiology *18,* 640-644 (2005).

[24] S. E. Milne, G. N. Kenny and S. Schraag, *Propofol sparing effect of remifentanil using closed-loop anaesthesia*. Br J Anaesth *90,* 623-629 (2003).

[25] M. Mahfouf, C. S. Nunes, D. A. Linkens and J. E. Peacock, *Modelling and multivariable control in anaesthesia using neural-fuzzy paradigms Part II. Closed-loop control of simultaneous administration of propofol and remifentanil.* Artif Intell Med *35,* 207-213 (2005).

[26] C. H. Ting, R. H. Arnott, D. A. Linkens and A. Angel, *Migrating from target-controlled infusion to closed-loop control in general anaesthesia.* Comput Methods Programs Biomed *75,* 127-139 (2004).

[27] A. R. Absalom and G. N. Kenny, *Closed-loop control of propofol anaesthesia using bispectral index: performance assessment in patients receiving computer-controlled propofol and manually controlled remifentanil infusions for minor surgery*. Br J Anaesth *90,* 737-741 (2003).

[28] S. Locher, K. S. Stadler, T. Boehlen, T. Bouillon, D. Leibundgut, P. M. Schumacher, R. Wymann and A. M. Zbinden, *A new closed-loop control system for isoflurane using bispectral index outperforms manual control.* Anesthesiology *101,* 591-602 (2004).

[29] A. Casati, M. Putzu and F. Vinciguerra, *A clinical comparison between bispectral index (BIS) and high frequency EEG signal detection (SNAP).* Eur J Anaesthesiol *22,* 75-77 (2005).

[30] G. N. Schmidt, P. Bischoff, T. Standl, G. Lankenau, A. Hellstern, C. Hipp and J. Schulte-am-Esch, *SNAP index and Bispectral index during different states of propofol/remifentanil anaesthesia.* Anaesthesia *60,* 228-234 (2005).

[31] C. A. Wong, R. J. Fragen, P. C. Fitzgerald and R. J. McCarthy, *The association between propofol-induced loss of consciousness and the SNAP index*. Anesth Analg *100,* 141-148 (2005).

[32] American Society of Anesthesiologists, *Practice advisory for intraoperative awareness and brain function monitoring.* Anesthesiology *104,* 847-864 (2006).

[33] M. M. Struys, T. De Smet, S. Greenwald, A. R. Absalom, S. Binge and E. P. Mortier, *Performance evaluation of two published closed-loop control systems using bispectral index monitoring: a simulation study*. Anesthesiology *100,* 640-647 (2004).

[34] E. Waterhouse, *New horizons in ambulatory electroencephalography*. IEEE Eng Med Biol Mag *22,* 74-80 (2003).

[35] K. N. Fountas, J. R. Smith, A. M. Murro, J. Politsky, Y. D. Park and P. D. Jenkins, *Implantation of a closed-loop stimulation in the management of medically refractory focal epilepsy: a technical note*. Stereotact Funct Neurosurg *83,* 153-158 (2005).

[36] S. Jezernik, R. G. Wassink and T. Keller, *Sliding mode closed-loop control of FES: controlling the shank movement*. IEEE Trans Biomed Eng *51,* 263-272 (2004).

[37] S. Ferrante, A. Pedrocchi, M. Ianno, E. De Momi, M. Ferrarin and G. Ferrigno, *Functional electrical stimulation controlled by artificial neural networks: pilot experiments with simple movements are promising for rehabilitation applications.* Funct Neurol *19,* 243-252 (2004).

[38] D. J. Eleveld, J. H. Proost and J. M. Wierda, *Evaluation of a closed-loop muscle relaxation control system*. Anesth Analg *101,* 758-64,table (2005).

Appendix C: Blood pumps to assist heart function

C.1 Background clinical use and indications

Heart failure is an increasing health problem worldwide. It is a complex clinical syndrome. Commonly it is defined as a disease characterised by a decline in the heart's ability to pump blood around a person's body at normal filling pressures to meet its metabolic needs. When heart failure occurs, the heart usually tries to compensate through changes in systemic vascular resistance and redistribution of blood flow (1). Although the heart may be capable of maintaining cardiac output at rest through such changes, it is unlikely to be able to cope with the increased demands that may result from normal exercise. The demands and stresses on the cardiovascular system tend to lead to further decline and, without effective treatment, to severe cardiac insufficiency, i.e. end-stage heart failure, and eventually death. End-stage heart failure is associated with major disability and a poor prognosis (2;3). Heart transplantation has become an accepted form of surgical treatment for people with end-stage heart failure, improving survival and patient quality of life. However, with continued decreases in organ donations, it is an option available to few.

Blood pumps have attracted increased interest and gained widespread acceptance as therapeutic instruments for the treatment of end-stage heart failure. These medical devices were initially developed for the temporary support for patients with end-stage heart failure until a donor heart could be found. This intended use was termed bridge to transplantation (BTT) (4;5). Currently, blood pumps are routinely implanted in patients who are eligible for transplantation. Prolonged blood pump support in the BTT setting revealed in some patients the propensity of the myocardium to recover, allowing removal of the medical device rather than previously necessary heart transplantation. This remarkable recovery is termed bridge to recovery (BTR) (6;7). The duration of the blood pump support for those who recover varies from days up to one year. The increasing duration of device implantation has led to the question of the suitability of implantable blood pumps for permanent use as an alternative to heart transplantation, often referred to as long-term chronic support (LTCS) or destination therapy (6). This may have the advantage of earlier intervention and rehabilitation of patients with end-stage heart failure, and avoids the risks associated with immunosuppression and organ rejection following heart transplantation. The use of blood pumps as LTCS is relatively new and uncertainty remains as to the duration of the support possible.

A substantial part of patients requiring long-term left ventricular support also have right ventricular complications which may lead to complete cardiac failure. Left ventricular support is not sufficient in these patients and either transplantation or the use of a permanent heart replacement system is indicated.

C.2 General blood pump classification

Blood pumps can be classified in two main categories:
- The ventricular assist device (VAD) which is implanted to assist the natural heart leaving the patient's own heart in place and still functioning. VADs support either left (LVAD) ventricle or right (RVAD) ventricle, or both as biventricular assist device (BiVAD).
- The permanent heart replacement system or total artificial heart (TAH) which replaces the explanted natural heart in terms of anatomical placement and function.

VADs have entered the clinical arena as:
- Displacement (or pulsatile flow) devices or,
- Rotary (or continuous flow) devices, which are sub-classified in:
    - Axial flow blood pumps,
    - Centrifugal or radial flow blood pumps,
    - Diagonal flow blood pumps or mixed flow systems (mainly used as extracorporeal devices for cardiopulmonary bypass systems).

There are differences in the configuration of the blood pumps in terms of the position of the pump (extracorporeal, paracorporeal or intracorporeal), implantation position (intra-abdominal, intraperitoneal, or preperitoneal pocket), method of driving the mechanism (pneumatically, electrically, magnetically driven), type of power source (wall-mounted, console-based or battery packs), positioning of the cannulae and leads delivering the power, valve structure, and the nature of the internal surfaces of the devices. Intracorporeal blood pumps are either connected by percutaneous leads through the patient's skin or totally implanted.

When considering pump design theory, axial flow blood pumps generate high flows at low pressure differences, whereas centrifugal flow pumps are capable of producing higher pressures at lower flows. Diagonal flow pumps tend to have the capability of high-generated pressures and high flow rates. Axial flow blood pumps, although far more compact than centrifugal pumps, operate at much higher rotational speeds to produce the desired head pressure and flow. Because of their small size and tubular configuration, axial pumps require less time to implant, thereby decreasing the costs and invasiveness of the procedure. Centrifugal pumps typically weigh more than axial flow pumps, and this may lead to patient discomfort after installation. In addition, axial flow blood pumps generally consume less power, which allow for more compact and lighter power supply components and eventually implantable batteries.

To date, most blood pumps are produced in the USA, but currently some European companies have caught up with continuing technological developments, and achieved important advantages in miniaturisation, magnetic levitation, low power use, and ease of implantation of pumps, e.g. percutaneous catheter delivery of intracardial devices. Furthermore, necessary monitoring and therapeutic interventions remain to be clarified and standardised.

Due to the large number of different pumps, which are already in clinical use or under development, the following section includes only a brief description of a selection of blood pumps. Extracorporeal devices are excluded. The presented collection of technical data, development data (e.g., clinically evaluated, animal testing, bench testing, design development) and regulatory approval status are neither complete nor consistent.

C.3 First-generation VADs – Displacement blood pumps

Displacement blood pumps are connected to the patient's left ventricle and provide circulatory support by taking over the workload of the failing heart. An inflow conduit directs blood from the left ventricle into the blood pump. The external control system triggers pumping by a pusher plate or diaphragm mechanism. The pump ejects blood through an outflow conduit into the body's arterial system via the aorta or arterial system. Bioprosthetic heart valves dictate the direction of flow. This mechanism mimics the native left ventricle by providing a pulsatile stroke volume while the patient's own left ventricle is off-loaded.

The most widely used displacement, pulsatile, devices have been extracorporeal devices such as the BVS® 5000 VAD of Abiomed, Inc. (Danvers, MA, USA) and the Thoratec VAD of

Thoratec Corporation (Pleasanton, CA, USA), and intracoporeal devices such as the Novacor® LVA System of WorldHeart, Inc. (Oakland, CA, USA), the HeartMate IP and VE/XVE of Thoratec Corporation. Although the large external pneumatic consoles of the first-generation displacement blood pumps have been replaced by implantable electric systems with a portable controller and power source, the serious problems of device weight (e.g., approximately 1.5 kg for the HeartMate XVE), size, noise, driveline infection and thromboembolism persist. Consequently, newer displacement devices are totally implantable systems without the need for percutanenous power or communication in an attempt to solve some of these issues, e.g. LionHeart™ VAD.

LionHeart™ VAD
The LionHeart™ VAD of Arrow International, Inc. (Reading, PA, USA) is a totally implantable LVAD system designed for LTCS (8). Implanted components are blood pump, system controller including rechargeable batteries, compliance chamber, and a (non-invasive) transcutaneous energy transmission (TET) system. The absence of percutaneous leads or connectors results in a reduction in the risk of infection, improved mobility, and enhanced quality of life.
The pump consists of a titanium case with motor, seam-free polyurethane blood sac, pusher plate, and unidirectional inlet/outlet mechanical heart valves. The motor actuates a roller screw and attached pusher plate. Linear motion of the screw results in reciprocating compression of the blood sac against the case via the attached pusher plate.
The controller is housed in a titanium case with a set of rechargeable batteries providing emergency power supply and allowing uncoupling of the external power supply for approximately 30 minutes. The controller regulates power from the external power supply and provides motor control and telemetry. The control system is dependent on continuous monitoring of end-diastolic volume (by means of Hall effect sensors mounted within the assembly case of the pump), thus determining the filling volume of the pump. Pumping characteristics are automatically adjusted to ensure complete filling of the pump by a software algorithm which is achieved through changes to the pump speed. An ongoing history of support characteristics is recorded and may be intermittently accessed by using the telemetry module that is included as part of the control system.
The gas-filled compliance chamber consists of a circular polymer sac and an attached subcutaneous infusion port system. Intermittent monitoring of the system pressure via the infusion port allows introduction or removal of air from the system, which is accomplished through the same port.
The external components include the power pack, power transmitter, and charger with battery packs, telemetry wand, system monitor, and various power supply options. External direct current (DC) power is converted to an alternating current (AC) allowing TET from the external primary power coil located over an implanted secondary power coil. This energy source is subsequently rectified to a DC that drives the motor, electronic hardware, and recharges the implanted batteries.
The pump and controller are placed in a preperitoneal pocket and the inlet tube of the pump is passed through an opening in the diaphragm and placed in the left ventricle. The outlet graft is anastomosed to the ascending aorta. The secondary power coil of the TET system is subcutaneously implanted in the right sixth-intercostal-space and the electrical connections are tunnelled to the controller and connected. The compliance chamber is placed in the pleural space and its inlet/outlet tube is tunnelled to the pump housing and connected. A small incision over the lower anterior chest is used to fashion a subcutaneous tissue pocket for the infusion port. This is inserted and tunnelled into the compliance chamber.

In November 2003 the LionHeart™ was the first LVAD to receive CE-marking for LTCS for patient with end-stage heart failure.
Technical data:

- Pump: size 71×69 mm, weight 680 g, stroke volume 64 ml, flow rate 8 l/min.
- Controller: size 102×95×29 mm (length×width×height), weight 500 g.
- TET internal coil: size 73×16 mm (diameter×thickness), weight 136 g.
- Compliance chamber: size 127×13 mm (diameter×thickness), weight 91 g.

Novacor® LVA System and Novacor® II
The Novacor® LVA System of WorldHeart, Inc. (Oakland, CA, USA) is a wearable, intracorporeal, electromechanical vented LVAD, with externally located controller and batteries (9;10). The connection is made with a percutaneous lead that contains electrical wires and a vent tube. The pump design is a dual-plate pusher type. The system continued to evolve and recently the inflow conduit made from an expanded polytetrafluoroethylene (ePTFE) was released and clinically evaluated (11). This inflow conduit successfully reduced thromboembolic complications and additional improvements of the system consisted of the addition of vibration damping and isolation elements into the pump driving unit, controller software refinement, and improvement in the battery capacity. The system can be operated in the fixed-pulse rate, synchronous or automatic (fill-to-empty) mode. In addition, the control system allows the patient to enjoy normal activities without manual intervention. The Novacor® LVA System is implanted in the abdominal space. Anticoagulant therapy must be administered, as in many other devices, in accordance with the regimen provided by the manufacturer.
Novacor® II is a miniaturised extension of the current Novacor® technology that substantially reduces pump size. The Novacor® LVA System pump is replaced by two small sac-type pumps, each driven by a central pusher plate mechanism, supporting the left ventricular output through multiple pump cycles. The pusher plate is driven by direct electro-magnetic actuation, with no bearings or other wearing mechanisms.
In Europe the Novacor® LVA System is intended for BTT, BTR, and LTCS. In the USA the system received FDA approval for BTT. The first chronic animal studies with the Novacor® II commenced in spring 2006.
Technical data Novacor® LVA System: weight 860 g, external volume 400 cm³, stroke volume 70 ml, flow rate 10 l/min.

C.4 Second-generation VADs

The rotary pumps (second-generation VADs), particularly the axial flow impeller pumps, have been developed following the encouraging results reported from the use of pulsatile devices, with the aim of circumventing some of the shortcomings of these devices such as their size, complexibility of mechanism, difficulties of implantation, durability and mechanical failures.
The innovative rotary pumps provide continuous, non-pulsatile flow using an electromagnetic mechanism consisting of a rotor with impeller blades which are the only moving parts rendering the patient pulseless. This raises the issue of pulseless circulation, one that has remained unsettled for a number of years (12;13). However, it should be noted that if the flow delivered by the pumps is continuous, the pressure curve of the aorta may remain pulsatile if the ventricle remains ejecting. Depending on the strength of the heart's native contractility and the resulting changes in pressure between the left ventricle and the aorta, pulsatile flow

may occur (14). Despite some unanswered questions these innovative designs are appealing due to their small size.

The continuous blood flow eliminated the need for valves, an internal compliance chamber, or an external vent. The pump design is compact. The control systems and power delivery mechanisms are easily portable and manageable by the patient. Rotary blood pumps have major advantages over pulsatile flow (displacement) pumps, including:

- Small size,
- Fewer moving parts,
- Absence of valves,
- Elimination of a variable volume device (compliance chamber) or external vent tube,
- Lower power consumption,
- Quiet operation,
- Lower cost,
- Fewer infections,
- Fewer thromboembolic complications,
- Eligible for extended use, nominal life expectancy is estimated to be approximately five years,
- Can be used in small patients with a body surface area of less than 1.5 m².

Potential disadvantages are:

- Complex feedback control mechanism,
- High afterload sensitivity,
- Low preload sensitivity, inseparable from afterload sensitivity because of continuous flow,
- Limited pump output if physiological control problems are solved by using only partial assist,
- Reduced pulsatility,
- Potential thrombosis caused by unnatural flow patterns,
- Chronic anticoagulation is necessary
- Some degree of haemolysis is common.

C.4.1 Axial flow blood pumps

DeBakey VAD®

The DeBakey VAD® of MicroMed Cardiovascular, Inc. (Houston, TX, USA) was developed in collaboration with NASA (15). NASA engineers, who were experienced in developing pumps for moving fluids such as rocket fuel, developed the mechanical and fluid dynamics capabilities. The pump is composed of a titanium pump housing, inlet cannula, rotating inducer impeller, Dacron outflow graft, stationary flow straightener, flow probe, and percutaneous cable assembly with controller connector. The inducer impeller is supported at both ends by double pivot bearings. The impeller has six blades with eight magnets hermetically sealed in each blade and rotated by electromagnetic force. The pump is driven by a brushless, DC motor stator that is contained in the stator housing. For pump implantation, a median sternotomy incision is performed. The pump is placed into an abdominal pocket and attached to the titanium inlet cannula that is placed into the apex of the left ventricle. The graft is connected to the pump outlet and anastomosed to the ascending aorta. The ultrasonic flow probe placed on the outflow graft confirms the bypass flow directory. The percutaneous line exits the skin from the abdominal wall and is connected to the wearable controller and battery packs providing power for up to eight hours. The controller module has audible and visual alarms with messages and prompts displayed on the

controller module's scrollable liquid crystal display. The system is designed to be simple to operate by both the patient and the clinician.

The DeBakey VAD® received the CE mark for BTT and LTCS in 2001. Currently, two pivotal phase III clinical investigations, one for BTT and the orther for LTCS, are being conducted in the USA.

Technical data: weight 95 g, size 86×25 mm (length×diameter), external volume 37 cm³, flow rate 5-10 l/min, rotational speed 7500-12,000 rpm, power requirement 6 W.

FlowMaker®

The FlowMaker® of Jarvik Heart, Inc. (New York, NY, USA), formerly known as Jarvik 2000, is one of the smallest axial flow devices possessing miniature mechanical bearings immersed in blood (16-19). Because of its small size, the FlowMaker® is placed into the apex of the left ventricle, and no inlet cannula is needed. The device consists of an impeller located in the centre of a titanium housing. The impeller consists of a neodymium-iron-boron magnet and two hydrodynamic titanium impeller blades that are suspended by two ceramic bearings. All the blood-contacting surfaces are made of a smooth mirror-finish surface of titanium. The motor receives power from an external controller. The pump speed is regulated by a pulse width-modulated brushless DC motor controller, which enables the impeller to rotate at various speeds. The pump's outflow graft is anastomosed to a graft placed on the ascending or descending aorta depending on the implantation technique used, i.e. median sternotomy or left thoracotomy. The permanently implantable model is responsive to heart rate and the rotational speed can be manually adjusted in increments of 1000 rpm according to the needs of the user. Two designs for the power delivery are available. As BTT the device is managed by an abdominal percutaneous line that connects to a small battery pack / controller worn at the waist or in a small shoulder bag. For patients receiving it as an implant for LTCS, the power connection is implanted behind the ear (posterior skull-mounted pedestal). This is like the system used for cochlear implants. The control unit monitors the pump function and the remaining power in the batteries. Audible and visual alerts notify the user of any problems.

The FlowMaker® was granted the CE mark for BTT and LTCS in May 2005.

Technical data: weight 85 g, size 55×25 mm (length×diameter), external volume 25 cm³, rotational speed 8000-12,000 rpm, flow rate 2-7 l/min at a pressure of 100 mm Hg, power requirement 3-7 W. A smaller paediatric version measures one-fifth of the dimensions of the adult device, weighing 18 g and displacing 5 ml.

HeartMate II

The HeartMate II of Thoratec Corporation (Pleasanton, CA, USA) is designed for LTCS in patients with end-stage heart failure (20;21). The pump unit has blood immersed mechanical bearings, connected with an abdominal percutaneous electrical lead to an external power source such as a battery-powered or an AC-supplied power driver. The impeller included three airfoil-shaped vanes to guide the flow through the pump. The well-designed blood pattern inside is achieved by computational fluid dynamics (CFD) and laser flow visualisation for the reduction of undesirable features such as thrombosis and haemolysis. The most recent version has a smooth and textured design for its blood contacting surfaces and succeeded to eliminate the thrombus at the inlet and outlet stators, which was previously observed (22). Under normal conditions, the rechargeable batteries provide power for two to four hours. A median sternotomy is performed and the pump is placed intra-abdominally. The inlet cannula is placed through the diaphragm in the ventricular appendage and the outflow cannula is connected to a Dacron graft, which is anastomosed to the ascending aorta. The speed control of rotation is chosen from manual or auto mode. In the auto mode, the motor

speed is controlled based on the algorithm using the pump's head pressure (H), pump flow (Q), and current consumption (I) characteristics. The pulsatility index that is derived by the predicted flow from the H-Q-I relationship is responsible for the control of the speed of the auto mode (20).

In November 2005, the HeartMate II was CE-marked for BTT and LTCS. Currently, the device is undergoing phase II pivotal clinical investigations in the USA for BTT and LTCS. Technical data: weight 350 g, size 60×43 mm (length×diameter), external volume 63 cm³, flow rate up to 10 l/min, rotational speed 6000-15,000 rpm, displacement volume 124 ml.

Impella Recover® system
The Impella Recover® system of Impella CardioSystems AG (Aachen, Germany) is based on a platform technology intended for short-term circulatory support for up to seven days (23;24). The system contains a family of intracardial micro-axial flow blood pumps (catheter-type devices) and has the potential of being widely accepted for rescue therapy, postsurgical circulatory support, and most likely in cardiology interventions in the USA, Europe, and soon in Japan. Patients who do not recover by the Impella Recover® can be bridged to more advanced implantable rotary blood pumps. The Impella Recover® system consists of implantable Recover® LD, RD and LP pumps, a mobile console for controlling the system (weight 3 kg, size 30×30 cm), and a purge for continuous rinsing of the pump. Miniature pressure sensors, only a few tenths of a millimetre, are used for control purposes. The console can be operated with rechargeable batteries for at least one hour. LD and RD pumps are inserted directly into the heart requiring thoracotomy. The Recover® LD is inserted via the ascending aorta by means of grafting and advanced through the aortic valve into the left ventricle. The Recover® RD is used to provide right ventricular support. Recover® LP pumps do not require thoracotomy. Recover® LP 5.0 is implanted via a small cut-down of the femoral artery and the Recover® LP 2.5 is implanted percutaneously via an introducer inserted in the femoral artery and advanced into the left ventricle using a guide wire.

The Impella Recover® system received the CE mark in December 2004.

Technical data: weight 8 g (LD) - 17 g (RD), length 30 mm, diameter 4 mm (or 12 F for LP 2.5), flow rate up to 2.5 (LP 2.5) - 5 (LD/LP 5.0) l/min, rotational speed up to 30,000 rpm, power requirement 10 W.

C.4.2 Centrifugal flow blood pumps

Centrifugal or radial flow blood pumps are somewhat larger than axial flow devices and provide non-pulsatile flow, but the rotational speeds are much slower (about 2000-4000 rpm). While the axial flow blood pumps have potentially the smallest size, the pressure/flow characteristics of a centrifugal flow blood pump are well suited to the requirements of mechanical circulatory support. Even with the impeller spinning at a constant speed, the flow through the pump varies with the difference between the upstream and downstream pressures. Thus the flow generated by the pump varies with the contraction of the native heart.

Gyro C1E3
The Gyro C1E3 of Kyocera Corporation (Kyoto, Japan) is a totally implantable centrifugal flow BiVAD (two-week pump) with two mechanical bearings (25). In 2003 the Gyro C1E3 has been evaluated in animal studies (26). Further information on the development of the Gyro C1E3 is lacking. The C1E3 evolved into the NEDO PI-601 pump (27). The current NEDO PI-710 pump (five-year pump) system includes a centrifugal pump with pivot bearings, a hydraulically levitated impeller, a rpm-controlled miniaturised actuator, an emergency clamp on the left outflow, and flow control. Animal studies are ongoing.

Technical data: flow rate 5 l/min at a pressure of 100 mm Hg and rotational speed of 1560 rpm.

C.5   Third-generation VADs

The main feature of the third-generation VADs is the replacement of mechanical bearings of the second-generation rotary pump design by hydrodynamic bearings and/or full magnetic-suspension pumps. Hydrodynamic bearings and magnetic levitation eliminate the contact bearing that supports the impeller in the second-generation devices allowing high reliability and durability (further features and needs are listed in Table C.1).

Table C.1. Desired features and needs in third-generation VADs (28)

Desired design feature	Specific clinical need
Broad application	Wide range of possible flows to accommodate: • Pump start-up off of bypass (low-end) • Wide range of patient activity (high end) • Reduced flow during recovery Expanding range of indicatons: • Bridge to transplant • Bridge to recovery or explant • Long-term circulatory support Broad range of patient population – no severe size restrictions
Durability of more than 5-10 years	Lower morbidity and mortality associated with devices replacement Lower rates of device-related failures and complications
Biocompatibility enhancements	Further reduce thrombus formation and embolic events Reduce anticoagulation requirements Minimize blood element injury/activation and infections
Quality-of-life features	Address: • Size • Noise • Vibration • Battery depletion • Large percutaneous leads • Ease of use, etc.
Ease of surgical implantation	Simplify implantation for safety and minimize operating room time
Cost-effective as compared to heart Transplantation	Required for widespread reimbursement

In a hydrodynamic bearing pump design the rotor is partially supported by a film of blood which helps counteract the mechanical loads on the pump rotor. In order for a hydrodynamic bearing to work, two conditions must be met:
- The rotor must be rotating at a speed sufficient to generate the film of blood and,
- The clearance gap must be small enough to allow for a film pressure high enough to create tilt to bear the loads of the impeller.

Great care must be taken to design the gaps to allow sufficient blood flow around the bearing to keep blood from stagnating and clotting.

In addition, the magnetic levitation design allows relatively large clearances around the impeller, permitting optimised flow around the impeller. This represents a significant advantage over mechanical and hydrodynamic blood bearings. Journal bearings represent a possible wear mechanism. The tight clearances and high shear rates associates with blood-washed bearings create the potential for damage to blood components of thrombus formation. These problems can be avoided with magnetic levitation of the impeller. The blood clearances around the pump rotor can be designed with haemocompatibility as top priority as opposed to any bearing requirement. Since there will be no wear due to the friction effect at

the contact bearings, life expectancy of third-generation blood pumps is expected to be beyond 10 to 15 years. In addition, the absence of actual physical contact between the impeller and its static components results in an almost silent device. Sensors linked to the magnetic bearing supply information about flow rate and pump performance used by the pulsatility control. The latest versions of the controllers employ an automatic antisuction algorithm preventing any suction through the pump in the left ventricle by detecting the residual pulsatility linked with it. The pump automatically adjusts its rotation speed and allows a renewed filling of the ventricle. The originally selected pump performance in then restored slowly and in a controlled way.

Magnetically levitated axial and centrifugal blood pumps are being developed in Europe, Japan, Australia and the USA. The most prominent examples are briefly described in the following section.

C.5.1 Axial flow blood pumps

INCOR® LVAD

The INCOR® LVAD of Berlin Heart AG (Berlin, Germany) is an axial blood flow device with a free floating active magnetic bearing of the axial impeller (29). Wear-free magnetic suspension bearings stabilise the impeller actively in the axial direction (by means of electric field forces) and passively in the radial direction (by means of magnetic field forces) without producing any actual physical contact between the impeller and its static components. A percutaneous driveline runs to an externally wearable controller for monitoring and controlling the system, and to a power pack, including two battery packs. Batteries can give patients up to 12 hours of mobility. Altogether, the external components weigh approximately 1.5 kg and can be transported inside a carrier next to the patient's body. The blood contact surfaces are coated by the Carmeda® process. This Carmeda® BioActive Surface contains covalently bound heparin. CFD was used to develop the optimal flow path. Flow information is obtained from integrated sensor system to measure the pressure of the head, and no additional flow meter is required. The device is equipped with an automatic anti-suction algorithm based on the grade of pulsatility of the blood flow across the pump. In case of impeding suction as detected by a decrease below a preselected grade of pulsatility, the speed of the pump is reduced by the algorithm. When the danger of suction-related pump stop has thus been overcome, the speed of the impeller is returned to the preset level. This modus prevents back flow through the pump. The pump housing is placed inside the pericardially cavity. The inflow cannula is anastomosed to the left ventricle and the outflow cannula to the ascending or descending aorta. Promising results have been reported from clinical experience in Germany (30).

The INCOR® LVAD received CE mark certification for use as BTT and BTR in April 2003. It is the first magnetically levitated axial blood flow pump that has moved into clinical practise in 2003 after a short development time.

Technical data: weight 200 g, size 123×30 mm (length×diameter), external volume 83 cm³, rotational speed 5000-10,000 rpm, flow rate 5-10 l/min, power consumption 0.6 W magnetic bearings, 3-4 W motor, 5 W electronics.

HVAD

The HVAD of HeartWare Ltd (Sydney, NSW, Australia) is one of the smallest third-generation blood pump under development as BTT and LTCS. Due to its small size, it is the only device implantable within the pericardial space. The pump design is a combination of an axial hydrodynamic support plus magnetic levitation. The first human implant in a clinical investigation for CE mark approval was performed in March 2006 in the Vienna General Hospital, Austria. Recently, HeartWare received approval from the Medicines and Healthcare

Products Regulatory Agency to start a clinical investigation in the UK. The completion of enrolment is envisaged before the end of 2006. This is expected to enable regulatory approval submission to be made during the first half of 2007, with regulatory approval anticipated during the second half of 2007.

Technical data: weight 145 g, external volume 45 cm³.

MicroVad

The MicroVad is currently under development at Helmholtz-Institute for Biomedical Engineering (Aachen, Germany) as a miniaturised VAD system, a so-called micro-axial blood pump intended for LTCS (31). It is very difficult to realise contact-free magnetic or hydrodynamic bearings for a micro-axial blood pump. Therefore, a hybrid-bearing solution was chosen which combines three different bearing concepts: mechanical, magnetic, and hydrodynamic. The axial bearing is a ceramic pivot bearing which centres the tip of the rotor in its position and serves partly as radial bearing. The bottom of the rotor is centred by the attracting forces of the magnetic coupling. Furthermore, the surrounding fluid flow acts as a hydrodynamic bearing, which additionally stabilises the rotor. The impeller is powered by a proximally integrated brushless micro-electronic motor. This unit is surrounded by a pump housing (7 mm in diameter) manufactured from polycarbonate enabling visual access to the fluid path inside the pump. The motor is completely immersed in blood within the pump housing. Therefore, the heat is completely dissipated by the surrounding blood and hot spots on the outer surface of the motor are prevented. A titanium inflow cage composed of a central opening and five additional openings within the cylindrical wall reduces the risk of wall suction. Because of its size (20×10 mm, length×diameter) the inflow cage can either be implanted in the left ventricular apex or into the left atrium. The outflow op the pump housing is connected to the descending aorta by means of an ePTFE graft.

The system underwent long-term durability tests, in vitro haemolysis tests, and thrombogenicity studies. Moreover, animal tests have been performed in adult sheep (31). Technical data: size 50×12 mm (length×diameter), rotational speed 30,000 rpm, flow rate 4 l/min at a pressure of 80 mm Hg.

MagneVAD I and II

The MagneVAD I of Gold Medical Technologies, Inc. (Valhalla, NY, USA) is an ultra-small magnetically levitated axial flow pump system (32). The MagneVAD I uses a magnetically suspended rotor requiring active axial control.

The MagneVAD II is an improved version of MagneVAD I (33). MagneVAD II is completely passive but otherwise similar. All passive bearing systems use either hydrodynamic or permanent magnets bearings. A self-washing radial hydrodynamic bearing suspends the rotor.

Technical data MagneVAD I: weight 82 g, size ~60×30 mm (length×diameter), external volume 25 cm³, flow rate 6 l/min at a pressure of 100 mm Hg and rotational speed of 12,500 rpm, power requirement 5 W for motor and 0.3 W for magnetic suspension.

C.5.2 Centrifugal flow blood pumps

EVAHEART™

The EVAHEART™ of Evaheart Medical USA, Inc. (Pittsburgh, PA, USA) is designed for BTT (34). The device consists of an internal pump with inlet and outlet cannulas, a console including controller and recirculating cooling system, and two rechargeable batteries for 8-10 hours continuous operation. The inlet and outlet cannulas are made of an ePTFE or polyester vascular graft. The inlet cannula is inserted into the apex of the left ventricle and the outlet cannula is connected to a graft anastomosed to the ascending aorta. Diamond-like carbon

coating or 2-methacryloxyethyl phosphorylcholine coating is applied to the blood contacting surface of the pump to improve haemocompatibility. A mechanical seal with recirculating colling system (Cool-Seal™) is used for shaft sealing. It is constructed of a SiC seat ring and carbon graphite seal ring. The seat ring is integrated with the stator of the hydrodynamic journal bearing to improve its structural stability. Inner seal faces are directly flushed by recirculating cooling fluid (pure sterile water) to improve convective heat transfer and prevent heat denaturation of blood proteins. Pure water introduced into the motor case through a purge inflow port lubricates the journal bearings, cools the motor coil and journal bearing, and flushes inner seal faces, then is returned to the outflow port. Cooling water is recirculated between blood pump and the controller through medical grade tubes. Cooling water consumption is very low (<0.04 ml/day). Cooling water is continuously purified and sterilised by an ultrafiltration filter incorporated in the controller. The controller with its displays and alarms is the user interface to the blood pump.

In Japan, the EVAHEART™ moved into clinical investigations for the evaluation of safety and reliability in 2005 (35). Two patients were implanted, one in May 2005 and the other in July 2005. In February 2006 these patients were successfully discharged home from the hospital.

Technical data: weight 370 g, size 55×64 mm (height×diameter), external volume 132 cm³, flow rate up to 12 l/min against 100 mm Hg pressure at a flow rate of 2600 rpm, power requirement 9-10 W.

VentrAssist LVAD

The VentrAssist LVAD of Ventracor Ltd (Chatswood, NSW, Australia) is designed for LTCS (36). The device has a contact-free hydrodynamicaly suspended impeller with an integrated rare earth magnet motor. The pump is encased in a biocompatible titanium alloy shell. Blood contacting surfaces are coated with a diamond-like carbon coating. Based on current battery technology, operation for periods of over eight hours is possible without battery changes. The pump is implanted below the diaphragm and is connected to the left ventricular apex and the ascending aorta using standard grafts. The abdominal percutaneous lead connects the internal pump to the controller and batteries worn on a belt.

Recently, the enrolment of the clinical investigation for CE mark approval has been completed.

Technical data: weight 298 g, size 60 mm in diameter, external volume 122 cm³, rotational speed 1800-3000 rpm, power requirement 7-8 W.

CorAide™ LVAD and DexAide RVAD

The CorAide™ LVAD of Arrow International (Reading, PA, USA) has a combination of a hydrodynamic and magnetic bearing system (37). The device is comprised of an implanted blood pump with inlet and outlet cannula, a percutaneous cable, an external portable electronic module, and Ni-metal hybrid battery packs providing approximately six hours for mobile operation. The pump is fabricated from titanium with a biocompatible surface coating. The rotating assembly does not require mechanical bearings, but utilises a combination of hydrodynamic and magnetic forces for its suspension and function. In combination with the passive magnetic support in the axial direction, the blood-lubricated fluid film stabilises the levitated positioning of the rotating assembly in the radial direction. The ascending blood flow of the blood-lubricated fluid-film washes the bearing surfaces and inhibits blood stagnation within the pump, contributing to the pump's nonthrombogenicity. An automatic control algorithm calculates a clinician-preprogrammed, patient-specific target pump flow based on the sensed rate and magnitude of pump flow pulsatility and on the calculated pressure drop across the inlet and outlet. This provides a physiologic feedback as to the

ventricular rate and contractility, the degree of unloading of the ventricle by the device, and the systematic arterial pressure afterload seen by the pump (38).

In 2003 the first patient with an implanted CorAide™ showed three days post-implant elevated haemolysis above normal to warrant replacement of the device. The clinical investigation was performed at the Diabetes and Heart Centre in Bad Oeynhausen (Germany). R&D activity elucidated the haemolysis problem and the clinical investigation was resumed in February 2005.

Technical data: weight 293 g, external volume 200 cm³, power requirement 6-7 W.

DexAide is an implantable right ventricular assist device (RVAD) and developed by modifying the design of the CorAide™ LVAD (39;40). The number of primary impellers is reduced from seven to five. Additionally, the size of each primary impeller is reduced and the volute housing is redesigned. Presently, only acute animal studies have been performed.

DuraHeart

The DuraHeart of Terumo Heart, Inc. (Ann Arbor, MI, USA) incorporates a 3D magnetically levitated centrifugal pump (41). The system consists of a titanium pumping unit, a titanium inflow and outflow conduit, wearable controller and battery packs, battery charger and hospital console. The pumping unit consists of an upper housing with the levitation system, impeller, and bottom housing. Three electromagnets and three position sensors are mounted in the upper housing. Tilting and axial displacements of the impeller are monitored and controlled using three degrees of freedom control. The levitated impeller is driven through a magnetic coupling force from the direct current brushless motor.

The first clinical investigation with the DuraHeart started in January 2004 in the Heart- and Diabetes Centre in Bad Oeynhausen (Germany) (42). Currently, DuraHeart is pending for CE mark approval.

Technical data: weight 540 g, size 45×72 mm (height×diameter), external volume 180 cm³, flow rate 2-10 l/min, rotational speed 1200-2600 rpm, power requirement 15 W (8-10 W for magnetic suspension).

HeartQuest VAD

The HeartQuest VAD of WorldHeart, Inc. (Oakland, CA, USA), uses a centrifugal pump, with a bearingless, magnetically levitated impeller (43). This magnetic levitation (Mag-Lev™) technology employs a unique combination of passive and active control. Other Mag-Lev™ blood pumps currently under development use active electromagnetic control for up to five axes of impeller position of tilt, with associated complex circuit and sensor requirements. The system uses permanent magnet support (passive suspension) in all of these axes but one. This patented hybrid design, with only a single axis of active control, yields an efficient and simple system. The blood contact surfaces are coated with a QuestCoat™ coating reducing the risk of coagulation. The blood pump is able to self-regulate by adjusting to patients' demands. The pump is placed in the left upper quadrant of the abdomen. The rigid titanium inflow cannula is sutured to the left ventricle apex. The outflow cannula is constructed from a reinforced vascular graft with an anastomosis at the ascending aorta. Animal studies have been performed in calves (28).

In early March 2006, the first human implant was performed at St. Luke's Hospital in Thessaloniki, Greece, marking the start of the feasibility clinical investigation.

Technical data: weight 440 g, size 35×75 mm (height×diameter), external volume 155 cm³, flow rate up to 10 l/min, rotational speed 2500 rpm, power requirement 12 W.

HeartMate III

The HeartMate III of Thoratec Corporation (Pleasanton, CA, USA) is a totally implantable uni-/biventricular assist system intended for alternative-to-transplant use operational for 10-15 years (44). The HeartMate III has the appearance of a disk-shaped blood pump. The pump casing, vent port, and inflow cannula are made of titanium alloy. The LVAD is based on bearingless motor technology and combines pump rotor, drive, and magnetic bearing functions in a single unit. The impeller is rotated and levitated with both active (three spatial degrees of freedom) and passive suspensions (three spatial degrees of freedom). Active control of rotational (θ_z) and radial position (X and Y) of the rotor is provided by feedback electronics, implemented by appropriately placed sensors. Axial position (Z) and tilting (θ_x and θ_y) are stabilised by passive magnetic forces. Control of the pump flow is by an auto-responsive algorithm based on various motor parameters.

Currently, the HeartMate III is under preclinical development.

Technical data: weight 475 g (535 g, including the inflow cannula, recovery section, outflow graft, bend relief, and all connecting hardware), size 30×69 mm (height×diameter), external volume 195 cm³, flow rate up to 10 l/min, rotational speed 2000-5500 rpm, power requirement 8 W.

MiTiHeart™

The MiTiHeart™ LVAD of Mohawk Innovative Technology, Inc. (Albany, NY, USA) is under development for LTCS (45). The pump design is based on a hybrid passive/active magnetic bearing system such that only one actively controlled axis is required. A reduction in the number of actively controlled axes reduces the power required to operate the bearings, thus increasing the operating time before battery change or recharge is required. Unique features of the design include a simple and direct path for main and wash flows, non-contacting operation of the pump rotor, and large clearance between pump rotor and housing. In addition, the pump use a redundant hydrodynamic thrust bearing which is not active during normal pump operation. Rather, the bearing is designed to prevent rotor contact under most severe transient loading conditions by sharing load carrying responsibilities of the magnetic bearing.. For example, transient loads that may be encountered if the patient falls accidentally. Additionally, the hydrodynamic thrust bearing provides emergency back-up support and, hence, fail-safe operation in the event of a failure of the magnetic thrust bearing. Currently, the MiTiHeart™ LVAD is being redesigned to reduce overall dimensions and incorporate a novel bio- and haemocompatible coating to further reduce the potential for thrombosis and haemolysis. Mohawk Innovative Technology, Inc. has also plans to conduct research and development jointly with other companies to develop the needed power supply and electronic controller used to monitor and adjust the pump speed as demanded by the patient's haemodynamic needs.

Technical data: weight 300 g, size 80×50 mm (height×diameter), flow rate 2-7 l/min, rotational speed 2500-3500 rpm, power requirement of the magnetically levitated system and motor <0.5 and 6 W, respectively.

C.6 Paediatric blood pumps

In early stages, hear failure in children is treated pharmacologically, as in adults, although there are comparatively few clinical trial data specific to children (46;47). As the disease severity increases, definitive therapy of heart failure in children consists of heart transplantation. Because sudden death in children awaiting heart transplantation is rare, the majority of deaths in this population are due to progressive heart and multi-organ failure and

are therefore, at least in theory, amenable to salvage therapy with mechanical circulatory support (48). A important difference between the use of blood pumps in adults and children is the suitability of the devices. For adults, there are many choices of devices designed specifically for these patients, whereas for children, the choices are limited. There is substantially less experience with paediatric VADs, including extracorporeal membrane oxygenation (a technique best preserved for short-term support and often associated with a high rate of complications). Options for longer-term support are the Thoratec pneumatic VAD (Thoratec Corporation, Pleasanton, CA, USA) (49;50), the EXCOR® Pediatric (Berlin Heart AG, Berlin, Germany) (51), and the MEDOS/HIA System (MEDOS Medizintechnik AG, Stolberg, Germany) (52). These devices are paracorporeal VAD systems employing pneumatically driven, thin membrane pumps to provide pulsatile flow and are available in a variety of pump sizes suitable for paediatric support. Nevertheless, paediatric mechanical support for children, infants, and neonates has started to attract more attention.

DeBakey VAD® Child
The DeBakey VAD® Child of MicroMed Technology, Inc. (Houston, TX, USA) is a miniaturised version of the DeBakey VAD® (53;54). The paediatric version employs the same axial flow pump used in the adult system with design modifications aimed at reducing the lateral space requirements for device implantation. These design modifications include a shortened inflow cannula with a more acute angle for the inflow tubing, a shortened plastic outflow graft protector, and reduced size of the flow probe on the outflow graft. Under the current Humanitarian Device Exemption programme of the FDA the DeBakey VAD® Child is used to provide temporary left ventricular support as a BTT for children from 5 to 16 years of age with a body surface area >0.7 m² and <1.5 m² and is designed to be implantable is this size range.

MVAD
The MVAD of HeartWare Ltd (Sydney, NSW, Australia) is expected to serve as the basis for the development of a paediatric VAD. The size of the MVAD is approximately one tenth the size of the HVAD (see above). Minimally invasive techniques are used to implant the MVAD as intravascular device. Currently, the MVAD is available for animal studies as a prototype. Animal studies commenced in August 2005. The first human clinical investigations are expected within approximately two years.

PediaFlow™ VAD
The PediaFlow™ VAD is being developed by a consortium consisting of the University of Pittsburgh (Pittsburgh, PA, USA), Carnegie Mellon University (Pittsburgh, PA, USA), Children's Hospital of Pittsburgh, LauchPoint Technologies LLC (Goleta, CA, USA), and World Heart Corporation (Oakland, CA, USA) (55;56). The PediaFlow™ is based on a mixed flow pump featuring a magnetically levitated impeller capable of providing left, right, or biventricular support for children 3-15 kg in weight (birth to approximately two years). The miniature paediatric-sized heart pump has a size of about a quarter. The PediaFlow™ can be used for up to six months and is fully implantable with a percutaneous lead for powering the device. A prototype has been designed and built for an *in vivo* implantation in an ovine animal model.
Technical data: size 10×15 mm (height×diameter), rotational speed 13,000 rpm at a pressure of 100 mm Hg, flow rate 0.3-1.5 l/min.

PediPump™
The PediPump™ is under development at the Cleveland Clinic (Cleveland, OH, USA) specifically for children (57). The PediPump™ is a mixed-flow device based on a magnetic bearing pump design to provide support for the entire range of patient sizes encountered in paediatrics with a single pump. The enabling technology is drawn from an adult catheter pump resulting in a new impeller VAD suitable for supporting children from newborns to adolescents. The pump rotating assembly consists of an impeller in the front, front and rear radial magnetic bearings, and a motor magnet in its centre. Blood enters axially at the inlet, and is turned in the impeller to exit the pump at an intermediate angle through the pump outside diameter. An inflow cannula is configured as appropriate for the size of the patient. Some arterial blood flows through windows at the rear of the pump under the influence of arterial pressure, washing and cooling the motor cap, before returning to the impeller. The rotor is supported on passive, radial magnetic bearings. Titanium shells seal all potentially corrodible components from blood and tissue. Unique features are the absence of a seal with suspension of the rotor on magnetic bearings resulting in high durability, and its small size (60×7 mm, length×diameter). Because of its small size, completely intravascular implantation may be possible for children beyond infancy. Furthermore, the device is suitable for left, right, and biventricular support. Animal testing is scheduled to commence in 2006.

Other devices
A paediatric VAD is under development at the University of Pittsburgh (Hershey, PA, USA) is a pulsatile flow device, based on the design of the adult-sized Pierce-Donachy VAD (Thoratec® #61650) and intended for BTT (expected maximum duration of use is six months). The infant-sized paediatric VAD has a dynamic stroke volume of approximately 13 ml. A larger 25 ml size for children is also planned. *In vitro* testing is being performed.
The Pediatric Jarvik 2000 of Jarvik Heart, Inc. (New York, NY, USA) is an axial flow blood pump in a child and infant model version. Initial animal testing has commenced. Currently, a paediatric model control system and battery is being developed. The child and infant models will be implantable in any of the four chambers of the heart for chronic mechanical left, right or biventricular support. Technical data child model: weight 17.8 g, length 5.5 mm, external volume 10 cm³, rotational speed 10,000-14,000 rpm, flow rate 0.5-3 l/min. Technical data infant model: weight 12 g, length 3.8 mm, external volume 4 cm³, rotational speed 16,000-24,000 rpm, flow rate 1.5 l/min.

C.7 Total artificial heart

Until recently, only pneumatic total artificial hearts (TAHs) with extracorporeal driving systems have been clinically used including prominent examples such as the Jarvik 7™ of Jarvik Heart, Inc. (New York, NY, USA) and its successor the CardioWest™ temporary TAH of SynCardia Systems, Inc. (Tucson, AZ, USA). These systems have been used as BTT, or in a few cases, as LTCS for patient with end-stage heart failure (58). Since July 2001, several patients have been implanted with a different type of TAH, a fully implantable prosthetic device.

AbioCor™ TAH and AbioCor II
The AbioCor™ TAH of Abiomed, Inc. (Danvers, MA, USA) is the world's first completely self-contained replacement heart. May 2004 the 14th patient received a prosthetic heart in the USA (59). The system is designed for LTCS enabling the patient to remain mobile and continue an active/productive lifestyle. After orthotopic implantation the device does not

require any percutaenous tubes or wires. Equipped with an internal motor, the AbioCor™ TAH is able to move blood through the lungs and the rest of the body, simulating the rhythm of the heartbeat.

The AbioCor™ TAH consists of both external and internal components. The internal components are the thoracic unit or pump, rechargeable battery, controller and TET coil. The thoracic unit consist of an energy converter and two pumping chambers that function as left and right ventricles. The energy converter is situated between the ventricles and contains a high-efficiency miniature centrifugal pump driven by a brushless DC motor. This centrifugal pump operates unidirectionally to pressurize a low-viscosity fluid. A two-position switching valve is used to alternate the direction of hydraulic flow between left and right pumping chambers. This results in an alternate left and right systole. The rate of the switching valve determines the beat rate of the device. There is a one-to-one correspondence between blood and hydraulic fluid displacement. The displacement of hydraulic fluid to one side results in the creation of a negative pressure in the opposite ventricle. Thus the device is considered an active fill device.

The internal controller, placed abdominally, drives the energy converter in the thoracic unit, monitors the implanted components, and transmits device performance data to a bedside console by means of radiofrequency telemetry. These radiofrequency transmissions from the internal controller to the external console convey information, including continuous real-time telemetry of hydraulic pressure waveforms, system operating parameters, battery status, component temperature, and alarm information. This information is stored for later retrieval and analysis. The internal rechargeable battery, also placed abdominally, is lithium ion based and functions as an emergency or backup power source. It is continually recharged by external power received through the internal TET coil and can provide up to 20 minutes of operation while disconnected from the main power source. The internal TET coil receives high-frequency power that is transmitted across the skin from the external TET coil. The internal TET coil system electronics covert this oscillating current to a DC that is used to power the thoracic unit and to recharge the internal batteries.

The four external components consist of an external TET coil, batteries, a TET module, and a bedside console. The bedside console is used during implantation, recovery, and when the patient is in his/her primary residence. The bedside console provides clinicians with a graphic user interface for control and monitoring the implanted system through radiofrequency communication. The console can be configured to operate in different modes for implantation, recovery, and home monitoring. In addition, the console can be remotely monitored when connected to a telephone jack through a laptop computer. The rechargeable battery in the console allows to be disconnected from AC power for brief periods without discharging the patient's internal battery. When the patient is ambulatory, the external TET coil is connected to the portable TET module. The TET module delivers energy to the TET coil from the external batteries and contains basic alarms systems that are activated if there is misalignment of the TET coil, low external battery voltage, or a general alarm indicating a potential problem with the system that is determined by re-establishing radiofrequency communication with the bedside console. The external batteries are lithium ion based and are able to provide up to one hour of support per pound battery allowing the patient to be completely free of the external power transmission for approximately four hours. The external batteries can either be carried in a vest or a handbag or attached to a Velcro belt.

Abiomed, Inc. is also working on the next generation implantable prosthetic device, the AbioCor II. Incorporating technology both from Abiomed, Inc. and Pennsylvania State University (Hershey, PA, USA), the AbioCor II is smaller (35% reduction in size) and therefore able to fit significantly more of the adult population, and is being designed with a goal of five year reliability.

Initially, Abiomed, Inc. submitted the AbioCor™ TAH for marketing approval under the Humanitarian Device Exemption to the FDA in September 2004. Abiomed, Inc. intends to submit for an FDA Investigational Device Exemption in 2006 in order to begin clinical investigations with a purpose of seeking premarket approval by 2008. Currently, the AbioCor II is being implanted in animal studies.

Technical data AbioCor™ TAH: weight ~900 g, beat rate 75-150 beats per minute, flow rate 4-8 l/min, rotational speed of centrifugal pump 3000-10,000 rpm.

ACcor TAH

The ACcor TAH of the Helmholtz-Institute for Biomedical Engineering, Aachen University of Technology (Germany), is being developed primarily for BTT and finally for use as a permanent heart replacement system. It consists of three main components: two diaphragms pump chambers, replacing the explanted ventricles functionally and anatomically, with inlet and outlet valves, and the electromechanical energy converter. The inlets of the pump chambers are connected to the natural atria while the outlets are connected to the aorta and the pulmonary artery, respectively. The energy converter consists of a brushless electronically commutated synchromotor and two reduction and hypocycloid gear units which transform the unidirectional rotational movement of the motor into translatory pusher plate excursions. Four acute animal tests in calves have been performed in cooperation with the university hospitals in Vienna (Austria) and Aachen (Germany). The ACcor TAH is capable of providing full circulation for 8.5 hours with a flow of 4-8 l/min.

A 20% smaller sized version of the ACcor TAH, the MiniACcor has been designed, manufactured and assembled. The MiniACcor pump unit is extensively tested within circulatory mock loops. The pump delivers flows between 4 to 7 l/min at aortic pressures of 80 to 140 mmHg at different pump rates. Currently, chronic animal experiments with the MiniACcor are being planned at the Radboud University (Nijmegen, The Netherlands) in cooperation with the Heart- and Diabetes Centre in Bad Oeynhausen (Germany) and the clinic for Thoracic- and Heart Surgery in Nijmegen.

C.8   Complications and risks

Haemorrhage, air embolism, progressive multi-system organ failure are the most common causes of early morbidity and mortality after placement of a blood pump. The most common complications in the late postoperative period are infection, thromboembolism, and failure of the devices (6).

Haemorrhage is the most common complication associated with placement of a VAD or TAH. It is related to the extensive surgical procedures required for device implantation (median sternotomy, cardiac mobilisation, and extensive dissection of the abdominal wall to create a pocket for implantation), coagulopathy caused by liver dysfunction, cardiopulmonary bypass-induced thrombocytopenia and platelet dysfunction, poor nutritional status, and anticoagulation therapy.

Although the incidence of severe right-sided heart failure (when LVAD is implanted) has been decreasing, mortality is still high once severe right heart failure occurs (60;61). Female sex, small body surface area, non-ischaemic aetiology, preoperative mechanical ventilation, circulatory support prior to LVAD insertion, low pulmonary artery pressure, and low right ventricular stroke work index are significantly associated with the need for RVAD use (61).

Infection is one of the most serious complications in the late postoperative period, and the risk of infection is largely related to a percutaneous energy cable or vents tube, as well as pump size (62). The infections at the exit site of the percutaneous lead are manageable with

local wound care and antibiotics. Infections in the abdominal wall pocket holding the device require more aggressive treatment, including open drainage, débridement, and rerouting of the drive line through a fresh exit site. Despite the widespread acceptance of several percutaneous VADs, only a fully implantable system can reduce the potential for infection and improve the quality of life necessary for LTCS.

Thromboembolism is related to device material as well as the flow pattern inside the device. The LionHeart™, Novacor, and AbioCor™ all use polyurethane blood contacting surfaces, and in some cases mechanical valves, mandating intensive anticoagulation therapy, without avoiding thromboembolism. Aggressive anticoagulation can cause late bleeding complications.

Haemolysis has been described with axial and centrifugal flow VADs (63). Haemolysis in pulsatile devices can be considered anecdotal. It is generally agreed that small axial flow blood pumps generate a higher haemolysis rate than larger centrifugal flow blood pumps. Axial flow devices work at higher rotational speeds (over 10,000 rpm, vs. 2000-4000 rpm for centrifugal devices), although in both designs the optimal design of the rotor and blades is critical to avoid significant destruction of circulating cells, as is the clearance between the impeller or turbine and the wall of the pump. This requires a long and complex phase of research and development to study the flow patterns inside various prototypes, and establish the relations with shear stress and hydraulic efficiency. The extensive use of computer simulations has accelerated such design developments and helped to define more precisely the optimal pump clearance and aspects of various surfaces and edges in contact with blood. Time-dependent CFD, particle image velocimetry, and CFD-based haemolysis predictions are three new engineering tools. Time-dependent CFD is used to analyse the complex flow field and shear stresses as blades of the impeller pass stationary components. The CFD results are validated both by steady-state pressure predictions as well as particle image velocimetry. Particle image velocimetry is an experimental method based on optically tracking particles suspended in a transparent blood analogue. Particles are illuminated by pulsed laser light timed to camera exposures. Flow velocities can be measured accurately and used to confirm the CFD results. Additionally, haemolysis can be predicted by coupling CFD to a tensor-based blood damage model. In this case, haemolysis is not predicted by the instantaneous stress, but is computed by the local deformation of the red blood cells. These new engineering tools can accelerate the design modifications and verifications process of blood pumps.

Mechanical failure is not very common during BTT, likely because of the short period of implantation (usually less than six months) (64). However, device durability and reliability are still major issues and limiting factors when current VADs are used for LTCS (8). The drawbacks of pulsatile devices are several. Pulsatile devices require valves in order to produce pulsatility. Valves are commonly reported to be sources of thromboembolic complications or structural failure, due to calcification or sepsis and subsequent risk of endocarditis. The presence of a valve prosthesis exposes the patient to more device-related complications and long-term reliability may be questioned. Implantable pulsatile devices are large and heavy and need to be implanted inside the body with large inflow and outflow grafts adjacent to a dilated heart in addition to the need of a fully implantable compliance chamber. The problem of size and anatomical fit in large abdominal pockets is critical. Surgeons often need to perform extensive skin incisions and generate significant abdominal wall trauma, leading to increased risk of abdominal wall pocket bleeding, recurrent large blood clot formation, and subsequent risk for chronic device and pocket infection. Extensive surgical trauma is associated with increased risk of multiple blood transfusions, development of respiratory distress syndrome, nosocomial infections, and eventually right heart failure.

The life expectancy for pulsatile devices is mainly dependent on the flex life of the diaphragm and on the reliability of the mechanism that activates this diaphragm. The Novacor® pump, which avoids any expansion of the diaphragm, has proven to be very reliable, showing three years of in vitro safe operation, confirmed by the quasi absence of failures in patients. So far, after over 1400 clinical implants, the Novacor® pump can be considered as a gold standard for mechanical reliability. There is no report of device failure with this pump, which is quite remarkable and unmatched.

In rotary blood pumps, the life-limiting component is the bearing system. Bearing-related problems have been a major obstacle for the development of axial and centrifugal flow devices. The bearings and seals are the most critical locations for platelet activation and thrombus formation. Sudden pump blockages with or without thromboembolic complications are not uncommon. Dry bearings in centrifugal flow pumps have been replaced by wet bearing systems (e.g., Jarvik's FlowMaker®), although bearings lubricated with blood may be a source of thrombus, with permanent need for heavy anti-coagulation. Heat generation in rotary blood pumps may also affect the function of vital parts of the activating system, in particular for bearing-supported pumps. Even if the power required to activate a rotary blood pump is much less than that for a pulsatile pump, the combination of heat generation and high shear stress close to seals and bearings may reduce both reliability and safety. Platelet aggregation can accelerate in these sensitive areas, the control of thrombus growth and the stabilisation of persistent depositions appear unpredictable. Consequently, one of the key technologies required for rotary blood pumps becomes the design of a magnetically levitated rotor.

Another issue is the avoidance of negative pressures at high rotational pump speeds, corresponding with totally non-pulsatile flows and full left ventricular unloading. This may lead to critical haemodynamic situations requiring manual intervention, which may be less acceptable in patients included in a home programme in spite of telemedicine utilisation.

In paediatric applications, the major source of morbidity after implantation continues to be neurological complications, including fatal incidences of stroke (49;65). A better understanding of the developmental changes in the coagulation cascade after implantation might facilitate a reduction in the high rate of bleeding and thromboembolic events during paediatric VAD support. In addition, research efforts into paediatric VAD technology must address biocompatibility issues to mitigate the risks arising from blood-surfaces interactions in these devices that may be unique to both lower flows and the paediatric patient. The introduction of paediatric-specific devices in recent years has brought this issue to the forefront. Right heart failure and biventricular failure in children may be due to more acute primary pathophysiologies that occur without the advanced systemic disease. In contrast, the progression right ventricular (biventricular) failure as a result of coronary artery disease or value disease in adults may suggest advanced and chronic disease that may be unresponsive to treatment with or without mechanical circulatory support.

Abbreviations

AC	alternating current
BiVAD	biventricular assist device
BTT	bridge to transplantation
BTR	bridge to recovery
CFD	computational fluid dynamics
DC	direct current
ePTFE	expanded polytetrafluoroethylene
LTCS	long-term chronic support
LVAD	left ventricular assist device
RVAD	right ventricular assist device
TAH	total artificial heart

TET	transcutaneous energy transmission
VAD	ventricular assist device

C.9 References, websites

References

(1) Smith JA, Rabinov M, Bergin PJ, Williams TJ, Anderson J, Esmore DS. Mechanical circulatory support: A necessary adjunct to a cardiac transplantation service. Transplant Proc 1992; 24(5):2004-2005.

(2) Ho KK, Pinsky JL, Kannel WB, Levy D. The epidemiology of heart failure: The Framingham Study. J Am Coll Cardiol 1993; 22(4 Suppl A):6A-13A.

(3) Køber L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliasen P, Lyngborg K et al. A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. N Engl J Med 1995; 333(25):1670-1676.

(4) Pennington DG, McBride LR, Kanter KR, Miller LW, Ruzevich SA, Naunheim K et al. Bridging to heart transplantation with circulatory support devices. J Heart Transplant 1989; 8(2):116-123.

(5) Portner PM, Oyer PE, Pennington DG, Baumgartner WA, Griffith BP, Frist WR et al. Implantable electrical left ventricular assist system: Bridge to transplantation and the future. Ann Thorac Surg 1989; 47(1):142-150.

(6) Goldstein DJ, Oz MC, Rose EA. Medical progress: Implantable left ventricular assist devices. N Engl J Med 1998; 339(21):1522-1533.

(7) Westaby S, Jin XY, Katsumata T, Taggart DP, Coats AJ, Frazier OH. Mechanical support in dilated cardiomyopathy: Signs of early left ventricular recovery. Ann Thorac Surg 1997; 64(5):1303-1308.

(8) El Banayosy A, Arusoglu L, Kizner L, Morshuis M, Tenderich G, Pae WEJr et al. Preliminary experience with the LionHeart left ventricular assist device in patients with end-stage heart failure. Ann Thorac Surg 2003; 75(5):1469-1475.

(9) Dagenais F, Portner PM, Robbins RC, Oyer PE. The Novacor left ventricular assist system: Clinical experience from the Novacor registry. J Card Surg 2001; 16(4):267-271.

(10) Deng MC, Loebe M, El Banayosy A, Gronda E, Jansen PGM, Vigano M et al. Mechanical circulatory support for advanced heart failure : Effect of patient selection on outcome. Circulation 2001; 103(2):231-237.

(11) Mussivand T, Hetzer R, Vitali E, Meyns B, Noirhomme P, Koerfer R et al. Clinical results with an ePTFE inflow conduit for mechanical circulatory support. J Heart Lung Transplant 2004; 23(12):1366-1370.

(12) Allen GS, Murray KD, Olsen DB. The importance of pulsatile and nonpulsatile flow in the design of blood pumps. Artif Organs 1997; 21(8):922-928.

(13) Saito S, Nishinaka T. Chronic nonpulsatile blood flow is compatible with normal end-organ function: Implications for LVAD development. J Artif Organs 2005; 8(3):143-148.

(14) Noon GP, Morley DL, Irwin S, Abdelsayed SV, Benkowski RJ, Lynch BE. Clinical experience with the MicroMed DeBakey ventricular assist device. Ann Thorac Surg 2001; 71(3 Suppl.):S133-S138.

(15) DeBakey ME. Development of a ventricular assist device. Artif Organs 1997; 21(11):1149-1153.

(16) Frazier OH, Myers TJ, Jarvik RK, Westaby S, Pigott DW, Gregoric ID et al. Research and development of an implantable, axial-flow left ventricular assist device: The Jarvik 2000 Heart. Ann Thorac Surg 2001; 71(3 Suppl.):S125-S132.

(17) Frazier OH, Myers TJ, Westaby S, Gregoric ID. Use of the Jarvik 2000 left ventricular assist system as a bridge to heart transplantation or as destination therapy for patients with chronic heart failure. Ann Surg 2003; 237(5):631-637.

(18) Frazier OH, Shah NA, Myers TJ, Robertson KD, Gregoric ID, Delgado R. Use of the Flowmaker (Jarvik 2000) left ventricular assist device for destination therapy and bridging to transplantation. Cardiology 2004; 101(1-3):111-116.

(19) Westaby S, Frazier OH, Pigott DW, Saito S, Jarvik RK. Implant technique for the Jarvik 2000 Heart. Ann Thorac Surg 2002; 73(4):1337-1340.

(20) Griffith BP, Kormos RL, Borovetz HS, Litwak K, Antaki JF, Poirier VL et al. HeartMate II left ventricular assist system: From concept to first clinical use. Ann Thorac Surg 2001; 71(3 Suppl.):S116-S120.

(21) Burke DJ, Burke E, Parsaie F, Poirier V, Butler K, Thomas D et al. The HeartMate II: Design and development of a fully sealed axial flow left ventricular assist system. Artif Organs 2001; 25(5):380-385.

(22) Frazier OH, Delgado III RM, Kar B, Patel V, Gregoric ID, Myers TJ. First clinical use of the redesigned HeartMate II left ventricular assist system in the United States: A case report. Tex Heart Inst J 2004; 31(2):157-159.

(23) Schmidt T, Siefker J, Spiliopoulos S, Dapunt O. New experience with the paracardial right ventricular axial flow micropump impella elect 600. Eur J Cardio-thorac Surg 2003; 24(2):307-308.

(24) Jurmann MJ, Siniawski H, Erb M, Drews T, Hetzer R. Initial experience with miniature axial flow ventricular assist devices for postcardiotomy heart failure. Ann Thorac Surg 2004; 77(5):1642-1647.

(25) Muramatsu K, Masuoka T, Fujisawa A. In vitro evaluation of the heparin-coated Gyro C1E3 blood pump. Artif Organs 2001; 25(7):585-590.

(26) Kawahito S, Maeda T, Motomura T, Takano T, Nonaka K, Linneweber J et al. Long-term ex vivo bovine experiments with the Gyro C1E3 centrifugal blood pump. ASAIO J 2003; 49(1):112-116.

(27) Nose Y, Furukawa K. Current status of the Gyro centrifugal blood pump--development of the permanently implantable centrifugal blood pump as a biventricular assist device (NEDO project). Artif Organs 2004; 28(10):953-958.

(28) Bearnson GB, Jacobs GB, Kirk J, Khanwilkar PS, Nelson KE, Long JW. HeartQuest ventricular assist device magnetically levitated centrifugal blood pump. Artif Organs 2006; 30(5):339-346.

(29) Hetzer R, Weng Y, Potapov EV, Pasic M, Drews T, Jurmann M et al. First experiences with a novel magnetically suspended axial flow left ventricular assist device. Eur J Cardio-thorac Surg 2004; 25(6):964-970.

(30) Schmid C, Tjan TDT, Etz C, Schmidt C, Wenzelburger F, Wilhelm M et al. First clinical experience with the Incor left ventricular assist device. J Heart Lung Transplant 2005; 24(9):1188-1194.

(31) Kerkhoffs W, Schumacher O, Meyns B, Verbeken E, Leunens V, Bollen H et al. Design, development, and first in vivo results of an implantable ventricular assist device, MicroVad. Artif Organs 2004; 28(10):904-910.

(32) Goldowsky M. Magnevad - The world's smallest magnetic-bearing turbo pump. Artif Organs 2004; 28(10):945-952.

(33) Goldowsky M, Lafaro R, Reed G. Magnevad status of design improvements human blood results and preliminary sheep trial. Artif Organs 2005; 29(10):855-857.

(34) Yamazaki K, Kihara S, Akimoto T, Tagusari O, Kawai A, Umezu M et al. EVAHEART: An implantable centrifugal blood pump for long-term circulatory support. Jpn J Thorac Cardiovasc Surg 2002; 50(11):461-465.

(35) Yamada K, Kihara S, Saito S, Tomioka H, Tsukui H, Kawai A et al. The EVAHEART an implantable centrifugal blood pump: Pre-IDE results and planned clinical trial in Japan. ASAIO J 2005; 51(2):39A.

(36) Watterson PA, Woodard JC, Ramsden VS, Reizes JA. VentrAssist hydrodynamically suspended, open, centrifugal blood pump. Artif Organs 2000; 24(6):475-477.

(37) Doi K, Golding LAR, Massiello AL, Kopcak MWJr, Gerhart RL, Schenk S et al. Preclinical readiness testing of the Arrow International CorAide left ventricular assist system. Ann Thorac Surg 2004; 77(6):2103-2110.

(38) Ochiai Y, Golding LAR, Massiello AL, Medvedev AL, Gerhart RL, Chen JF et al. In vivo hemodynamic performance of the Cleveland Clinic CorAide blood pump in calves. Ann Thorac Surg 2001; 72(3):747-752.

(39) Ootaki Y, Kamohara K, Akiyama M, Zahr F, Kopcak MWJr, Dessoffy R et al. Initial in vivo evaluation of the DexAide right ventricular assist device. ASAIO J 2005; 51(6):739-742.

(40) Fukamachi K, Horvath DJ, Massiello AL, Ootaki Y, Kamohara K, Akiyama M et al. Development of a small implantable right ventricular assist device. ASAIO J 2005; 51(6):730-735.

(41) Nojiir C, Kijima T, Maekawa J, Horiuchi K, Kido T, Sugiyama T et al. Terumo implantable left ventricular assist system: Results of long-term animal study. ASAIO J 2000; 46(1):117-122.

(42) El Banayosy A, Koerfer R, Hetzer R, Wieselthaler G, Pavie A. Initial results of a European multicenter clinical trial with the DuraHeart® Mag-Lev centrifugal left ventricular assist device. J Heart Lung Transplant 2006; 25(2, Supplement 1):145.

(43) Chen C, Paden B, Antaki J, Ludlow J, Paden D, Crowson R et al. A magnetic suspension theory and its application to the HeartQuest Ventricular Assist Device. Artif Organs 2002; 26(11):947-951.

(44) Loree II HM, Bourque K, Gernes DB, Richardson JS, Poirier VL, Barletta N et al. The HeartMate III: Design and in vivo studies of a Maglev centrifugal left ventricular assist device. Artif Organs 2001; 25(5):386-391.

(45) Locke DH, Swanson ES, Walton JF, Willis JP, Heshmat H. Testing of a centrifugal blood pump with a high efficiency hybrid magnetic bearing. ASAIO J 2003; 49(6):737-743.

(46) Kouatli AA, Garcia JA, Zellers TM, Weinstein EM, Mahony L. Enalapril does not enhance exercise capacity in patients after fontan procedure. Circulation 1997; 96(5):1507-1512.

(47)   Hoffman TM, Wernovsky G, Atz AM, Kulik TJ, Nelson DP, Chang AC et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. Circulation 2003; 107(7):996-1002.

(48)   Rosenthal DN, Dubin AM, Chin C, Falco D, Gamberg P, Bernstein D. Outcome while awaiting heart transplantation in children: A comparison of congenital heart disease and cardiomyopathy. J Heart Lung Transplant 2000; 19(8):751-755.

(49)   Reinhartz O, Keith FM, El Banayosy A, McBride LR, Robbins RC, Copeland JG et al. Multicenter experience with the Thoratec ventricular assist device in children and adolescents. J Heart Lung Transplant 2001; 20(4):439-448.

(50)   Hill JD, Reinhartz O. Clinical outcomes in pediatric patients implanted with Thoratec Ventricular Assist Device. Ped Card Surg Ann 2006; 9(1):115-122.

(51)   Etz C, Welp H, Tjan TDT, Krasemann T, Schmidt C, Scheld HH et al. Successful long-term bridge to transplant in a 5-year-old boy with the EXCOR left ventricular assist device. Thorac Cardiovasc Surg 2004; 52(4):232-234.

(52)   Kaczmarek I, Mair H, Groetzner J, Sachweh J, Oberhoffer M, Fuchs A et al. Mechanical circulatory support in infants and adults with the MEDOS/HIA assist device. Artif Organs 2005; 29(10):857-860.

(53)   Imamura M, Hale S, Johnson CE, Schmitz ML, Morrow WR, Fiser WP et al. The first successful DeBakey VAD child implantation as a bridge to transplant. ASAIO J 2005; 51(5):670-672.

(54)   Morales DL, Dibardino DJ, McKenzie ED, Heinle JS, Chang AC, Loebe M et al. Lessons learned from the first application of the DeBakey VAD Child: An intracorporeal ventricular assist device for children. J Heart Lung Transplant 2005; 24(3):331-337.

(55)   Wu J, Antaki JF, Wagner WR, Snyder TA, Paden BE, Borovetz HS. Elimination of adverse leakage flow in a miniature pediatric centrifugal blood pump by computational fluid dynamics-based design optimization. ASAIO J 2005; 51(5):636-643.

(56)   Wearden PD, Morell VO, Keller BB, Webber SA, Borovetz HS, Badylak SF et al. The PediaFlow^{TM} Pediatric Ventricular Assist Device. Ped Card Surg Ann 2006; 9(1):92-98.

(57)   Duncan BW, Lorenz M, Kopcak MW, Fukamachi K, Ootaki Y, Chen HM et al. The PediPump: A new ventricular assist device for children. Artif Organs 2005; 29(7):527-530.

(58)   Copeland JG, Smith R, Icenogle T, Vasu A, Rhenman B, Williams R et al. Orthotopic total artificial heart bridge to transplantation: Preliminary results. J Heart Transplant 1989; 8(2):124-138.

(59)   Dowling RD, Gray LAJr, Etoch SW, Laks H, Marelli D, Samuels L et al. Initial experience with the AbioCor Implantable Replacement Heart System. J Thorac Cardiovasc Surg 2004; 127(1):131-141.

(60)   Fukamachi K, McCarthy PM, Smedira NG, Vargo RL, Starling RC, Young JB. Preoperative risk factors for right ventricular failure after implantable left ventricular assist device insertion. Ann Thorac Surg 1999; 68(6):2181-2184.

(61)   Ochiai Y, McCarthy PM, Smedira NG, Banbury MK, Navia JL, Feng J et al. Predictors of severe right ventricular failure after implantable left ventricular assist device insertion: Analysis of 245 patients. Circulation 2002; 106(12 Suppl 1):I198-I202.

(62)   Myers TJ, Khan T, Frazier OH. Infectious complications associated with ventricular assist systems. ASAIO J 2000; 46(6):S28-S36.

(63)   Nakazawa T, Makinouchi K, Takami Y, Glueck J, Takatani S, Nosé Y. The effect of the impeller-driver magnetic coupling distance on hemolysis in a compact centrifugal pump. Artif Organs 1996; 20(3):252-257.

(64)   Navia JL, McCarthy PM, Hoercher KJ, Feng J, Jeevantham R, Smedira NG et al. Do left ventricular assist device (LVAD) bridge-to-transplantation outcomes predict the results of permanent LVAD implantation? Ann Thorac Surg 2002; 74(6):2051-2062.

(65)   Stiller B, Hetzer R, Weng Y, Hummel M, Hennig E, Nagdyman N et al. Heart transplantation in children after mechanical circulatory support with pulsatile pneumatic assist device. J Heart Lung Transplant 2003; 22(11):1201-1208.

Websites

Abiomed, Inc. (Danvers, MA, USA)
        www.abiomed.com
Arrow International (Reading, PA, USA)
        www.arrowintl.com
Berlin Heart AG (Berlin, Germany)
        www.berlinheart.com
Evaheart Medical USA, Inc. (Pittsburgh, PA, USA), subsidiary of Sun Medical Technology Research Corporation (Suwa City, Japan)
        www.evaheart-usa.com

HeartWare Ltd (Sydney, NSW, Australia)
    www.heartware.com.au
Impella CardioSystems AG (Aachen, Germany), recently acquired by Abiomed, Inc.
    www.impella.com
Jarvik Heart, Inc. (New York, NY, USA)
    www.jarvikheart.com
LaunchPoint Technologies LLC (Goleta, CA, USA)
    www.launchpoint.com
MicroMed Cardiovascular, Inc. (Houston, TX, USA)
    www.micromedtech.com
Mohawk Innovative Technology, Inc. (Albany, NY, USA)
    www.miti.cc
SynCardia Systems, Inc. (Tucson, AZ, USA)
    www.syncardia.com
Terumo Heart, Inc. (Ann Arbor, MI, USA), subsidiary of Terumo Corporation (Tokyo, Japan)
    www.terumo.co.jp
Thoratec Corporation (Pleasanton, CA, USA)
    www.thoratec.com
Ventracor Ltd (Chatswood, NSW, Australia)
    www.ventracor.com
WorldHeart, Inc. (Oakland, CA, USA)
    www.worldheart.com

Appendix D: Cardiac pacing and defibrillation devices

D.1 Cardiac pacemakers

A cardiac pacemaker is a small battery-powered device that is implanted permanently into the body intended for heart rhythm control in case the heart's natural pacemaker, i.e. the sinus node, is not functioning properly. A pacemaker is used when the heartbeats too slowly (bradycardia) or has other abnormal rhythms (arrhythmias). In some cases, pacemakers are also used to treat symptoms of heart failure. A pacemaker consists of three main components: the pulse generator, the lead, and a programmer. The pulse generator have become smaller over the years and often weighs less than 30 g with a volume of less than 15 cm³. The pulse generator has a sealed (lithium ion-based) battery within the same unit and an electronic circuitry package. Current batteries last about six to eight years on average. The electronic circuitry of the pulse generator produces electrical pulses that keep the heart beating at the correct pace. The pacemaker is connected to the heart through one to three leads (insulated wires) that are placed in or attached to the heart's chambers. Each lead has an electrode on its tip. The leads may also relay signals from the heart to the pulse generator. The third component of the system is the programmer which is like a desktop computer. The physician uses it to communicate with the pacemaker's software. The programmer checks also the status of the battery. Most pacemakers are demand pacemakers. They have a sensing device which turns off when the heart rate is above a certain level and turns back on when the heart rate is too slow.

Leading manufacturers of pacemakers are Guidant Corporation (St. Paul, MN, USA), Medtronic, Inc. (Minneapolis, MN, USA), St. Jude Medical, Inc. (St. Paul, MN, USA), and Vitatron BV (Arnhem, The Netherlands).

D.1.1 General pacemaker classification and features

Pacemakers can be classified in three broad categories:
- Rate-responsive pacemakers,
- Single-chamber pacemakers,
- Dual-chamber pacemakers,
- Cardiac resynchronisation therapy (CRT) pacemakers.

Rate-responsive pacemakers may be programmed to increase or decrease heart rate to match the demands. Single-chamber pacemakers use only one lead placed into the right atrium or right ventricle, dual-chamber pacemakers have two leads: one is placed in the right atrium and the second in the right ventricle. CRT devices have three leads. One in the right atrium, one in the right ventricle, and one is placed in the left ventricle via the coronary sinus or epicardially. CRT is when a pacemaker is used to coordinate the heart's four chambers to act synchronously, allowing the heart to pump more efficiently.

The pacemaker has two functions: pacing and sensing. Pacing is when the pacemaker sends electrical signals to the heart through the lead(s). Each electrical signal is called a pacing pulse and initiate the heartbeat. Sensing the heart's electrical system back to the pacemaker allows the pacemaker to not interfere with natural, healthy heart rate.

Health care professionals use Table D.1 to decipher the properties of pacemakers. The table lists the NASPE & BPEG generic codes for anti-bradyarrhythmia and adaptive-rate pacing, and anti-tachyarrhythmia devices (1).

Table D.1. NASPE and BPEG generic pacemaker codes

Position	I	II	III	IV	V
Category	Chambers paced	Chambers sensed	Response to sensing	Rate modulation	Multisite pacing
NBG code	O = None	O = None	O = None	O = None	O = None
	A = Atrium	A = Atrium	T = Triggered	R = Rate	A = Atrium
	V = Ventricle	V = Ventricle	I = Inhibited	modulation	V = Ventricle
	D = Dual	D = Dual	D = Dual		D = Dual
	(A+V)	(A+V)	(T+I)		(A+V)

NASPE is the North American Society of Pacing and Electrophysiology.
BPEG is the British Pacing and Electrophysiology Group.

D.1.2 Technological advances

Pacemakers have become increasingly sophisticated during their half-century of clinical use. The goal of these complex pacing systems is to reproduce the normal electrical activation of the heart. An increasing percentage of pacemakers incorporate sensors to detect states of exercise and trigger accelerations in pacing rate. In pacemaker patients who are chronotopically incompetent (i.e., unable to increase sinus node rate appropriately with exercise), these rate-responsive pacemakers allow for increases in pacing rates with exercise and have been shown to improve exercise capability and quality of life. The vast majority of sensors incorporated into rate-responsive pacemakers are piezoelectric crystals or accelerometers that detect body motion, vibration, or acceleration. Other technologies using sensors that measure minute ventilation or QT interval of an ECG may provide a heart rate response more proportional to exercise than piezoelectric sensors or accelerometers. An advantage of all these sensor technologies is that they do not require specialised pacemaker leads, although minute ventilation sensing requires a bipolar lead.

Rate-responsive pacemakers
Pacemakers generators that incorporate two rate-responsive sensors are commercially available. These dual-sensor pacemakers incorporate one sensor that rapidly responds to exercise, i.e. piezoelectric crystal or accelerometer), and one that responds more proportionally to increasing levels of exercise, i.e. minute ventilation or QT interval. Studies have shown more appropriate rate response to various types of exercise when information from two sensors is used than when a single sensor is used (2;3). The challenge of adjusting the response of these generators to exercise appropriately in patients is increasingly becoming recognised. To facilitate optimal programming of rate-responsive capability, many current generators incorporate procedures for initial programming of rate-responsive parameters, subsequent automatic adjustment of these parameters, and retrievable diagnostic data (such as heart rate histograms and heart rate plots) to assess the appropriateness of the rate response.

Single-lead VDD pacemakers systems
Despite advances in rate-responsive pacemakers, it is widely appreciated that the best signal to guide heart rate response to exercise (and other forms of physiologic stress) is a normal functioning sinus node. Most commonly, dual-chamber pacemakers incorporating separate atrial and ventricular leads are used to detect atrial depolarisation. Single-lead transvenous pacing systems that are capable of sensing atrial depolarisation are commercially available. The distal end of the lead is positioned in the right ventricle for ventricular pacing and sensing; a pair of electrodes is incorporated in the more proximal portion of the lead body lying within the right atrial cavity for atrial sensing. With current technology, single-lead VDD pacing systems are not capable of atrial pacing. The atrial signal sensed by single-lead VDD pacemakers has less consistent amplitude than that typically sensed by conventional dual-chamber pacemakers and varies significantly with posture, but sensing performance is generally satisfactory (4). Single-lead VDD pacemaker systems are an alternative to dual-lead

pacemakers in patients with atrioventricular block in whom atrial pacing is not required and in whom simplicity of implantation of two leads is desired.

Automatic mode switching
When non-physiologic atrial tachyarrhythmias, such as atrial fibrillation or flutter, occur paroxysmally in a patient with a dual-chamber pacemaker programmed to conventional DDD or DDDR mode, the tachyarrhythmia will generally be tracked near the programmed maximum tracking rate, leading to an undesirable acceleration of ventricular pacing rate. Newer dual-chamber generators incorporate algorithms for detecting rapid, non-physiologic atrial rates and automatically switches to one that does not track atrial activity, such as DDI or DDIR. When the atrial trachyarrhythmia terminates, the pacemaker automatically reverts back to the DDD or DDDR mode. This automatic mode switch feature is especially helpful in patients with atrioventricular block and paroxysmal atrial fibrillation and expands the usefulness of dual-chamber pacemakers in such patients.

Pacemaker leads
The majority of pacemakers use transvenous endocardial leads, with the remainder using epicardial leads. Transvenous leads may be bipolar or unipolar in configuration. Bipolar configurations have the advantage of avoiding myopotential inhibition and skeletal muscle stimulation, and an increasingly important advantage is that unlike most unipolar pacing systems, they are compatible with concomitantly implanted cardioverter-defibrillators. However, some manufacturers' bipolar leads have higher failure rates than their unipolar leads.
The insulation material used in pacemaker leads is either silicone rubber or polyurethane. Historically, some bipolar lead models with polyurethane insulation have shown unacceptable high failure rates due to degradation of the insulation. Many current polyurethane leads, using different polymers and different manufacturing processes, appear to be avoiding these unacceptable high failure rates.
Active fixation leads, in which the distal tip of the lead incorporates a small helical screw for fixation to the endocardium, are an alternative to passive fixation leads. Active fixation leads allow for more alternatives in the site of endocardial attachment. For instance, whereas a passive fixation ventricular lead generally must be positioned in the right ventricular apex, an active fixation lead may be position in the apex, outflow tract, or inflow tract of the right ventricle. Active fixation leads have an additional advantage of greater ease of extraction after long-term implantation. A disadvantage of active fixation leads is that they generally have higher chronic capture thresholds than do passive fixation leads, although this difference is minimised with the incorporation of steroid elution.
An important advance in pacemaker leads is the development of leads with lower capture thresholds, which result in reduced battery consumption during pacing. Steroid-eluting leads incorporate at their distal tip a small reservoir of corticosteroid that slowly elutes into the interface between the lead electrode and the endocardium, reducing the inflammation and fibrosis that normally occur at this interface. As a result, steroid-eluting leads have significantly lower long-term capture thresholds than leads not incorporating steroid. The benefit of steroid elution was originally demonstrated in passive fixation transvenous leads (5). The benefit has also been demonstrated in active fixation transvenous leads (6) and epicardial leads (7).

Giant magnetoresistive sensors
Another technological development is the pacemaker using giant magnetoresistive (GMR) sensors. GMR magnetic sensors are made of sandwiches of thin films consisting of

alternative layers of magnetic and non-magnetic materials. In these devices a conductive non-magnetic interlayer separates two magnetic layers. Combined this way, the materials' resistance to current is high. An external magnetic field causes the magnetic fields in all layers to line up in the same direction. Subsequently, electric resistance decreases dramatically. With their high degree of stability and sensitivity, the GMR sensors can replace more conventional magnetic sensor technologies. St. Jude Medical, Inc. (St. Paul, MN, USA) is manufacturing such a pacemaker. GMR sensors replace the reeds of conventional pacemakers. Pacemakers must be tuned to the specific needs of each person's body. Physicians sue magnetics to tune the pacemaker from outside the body. The device in the pacemaker that responds to the magnetic signals is usually a reed switch. GMR sensors can replace the reeds. They are solid-state devices and not mechanical. Benefits are high sensitivity (one order of magnitude or more than a reed), small size (1.2×1.3 mm), high impedance, and low power.

D.2   Implantable cardioverter-defibrillators

An implantable cardioverter-defibrillators (ICD) is a device designed to quickly detect a life-threatening, rapid heartbeat. It converts the abnormal rhythm back to normal by delivering an electrical shock to the heart. The basic components of ICDs have not changed over the past 20 years (8;9). The ICD consists of three main parts: the pulse generator or defibrillator, the leads with electrodes, and a programmer. The defibrillator has a number of components. A small sealed titanium metal case that contains a lithium-silver vanadium oxide battery, voltage converters and resistors, capacitors to store charges, microprocessors and integrated circuits to control the analysis of the rhythm and the delivery of the therapy, memory chips to store electrographic and other data, and a telemetry module. The top of the pulse generator contains an epoxy resin header for the attachment of leads. The metal case can be as small as 30 cm³ and can weigh as little as 50 g.
The ICD detects and automatically terminates ventricular tachyarrhythmias via electrical energy stored in the battery which may last up to seven years depending on the type and shocks delivered. ICD leads are constructed in a fashion similar to pacemaker leads, except that a shocking coil or coils are also included. Leads are specialised thin insulated wires connected to the defibrillator that carry electrical energy from the defibrillator to the heart and relay information about the heart's electrical activity back to the defibrillator. The external programmer is a specialised computer used for monitoring and adjusting instructions to the ICD.
Leading manufacturers of ICDs are similar to those of pacemakers (see above).

D.2.1 General ICD classification and features
ICDs can be classified in three broad categories:
- Single-chamber ICDs,
- Dual-chamber ICDs,
- Chronic resynchronisation therapy (CRT) ICDs.

Single-chamber ICDs have only a right ventricular lead, dual-chamber ICDs have a right atrial and right ventricular lead, and CRT devices also have an left ventricular lead that is placed via the coronary sinus or epicardially.
The essential features of ICD function include:
- Detecting tachyarrhythmia,
- Classification of a tachyarrhythmia as a treatable arrhythmia,
- Delivering therapy,

- Monitoring of heart rhythm after treatment,
- Storage of diagnostic results from the episode.

Sensing of tachyarrhythmia occurs via a dedicated bipole of small electrodes near the catheter tip (dedicated sensing) or via a bipole from the tip electrode to a coil electrode that is also used to deliver defibrillation shocks (integrated sensing). After appropriate detection, anti-tachycardia pacing may be initiated for appropriate rhythm disturbances, or a defibrillation shock may be delivered between a coil and the ICD generator box (active can). Arrhythmia detection can be based on purely on heart rate, as in early-generation devices, or on more sophisticated algorithms.

All current ICDs have a number of features that are not directly related to the analysis of or the delivery of therapy for ventricular arrhythmias. All models have a built-in pacemaker with pacing modes similar to those in single- or dual chamber pacemeakers. Pacing may be necessary to support the heart in some instances, for example, after a shock, or during a very slow heartbeat. The pacemaker also allows the device to correct heartbeats that are too fast. Information about battery voltage, lead impedance, and the time needed to charge the capacitor is stored for later analysis.

Implantation

Initially, ICD implantation was a major operation requiring thoracotomy and general anaesthesia. The defibrillator electrodes were patches sewn onto the myocardium, and leads were tunnelled subcutaneously to the device, which was implanted in a subcutaneous abdominal pocket. Modern ICDs are transvenous systems. The device is implanted either subcutaneously, as for a pacemaker, or subpectorally, in thin patients to prevent eroding the skin. Larger devices suitable for abdominal implants are available primarily as replacement generators in patients with pre-existing lead systems but are being phased out by manufacturers. The ventricular lead is positioned in the right ventricular apex (single-chamber ICD) at a site that can pace and also defibrillate the heart. A second lead can be positioned in the right atrial appendage to allow dual-chamber pacing if required and discrimination between atrial and ventricular tachycardias. The ventricular lead has either one or two shocking coils. During implantation the unit is tested under conscious sedation. Adequate sensing during sinus rhythm, ventricular tachycardia and ventricular fibrillation is established, and also pacing and defibrillatory thresholds. Defibrillatory thresholds should be at least 10 J less than maximum output of the ICD (~30 J) (10).

D.2.2 Technological advances

Over the last 10 years, there have been several important advances in ICD technology, particularly relating to the microprocessor, the reduction in size and the implant technique. For example, devices in the early 1990s typically had less than 1 kB of random access memory, compared with more than 512 MB today (11). Reduction in size by more than 80% during the past 15 years and evolution of more physiological shape reduce incision size and increase patient comfort. Also important is the development of the ability to record and store intracardiac electrograms. This allows the monitoring of each episode of anti-tachycardia pacing or defibrillation, including episodes immediately before and after tachycardia detection and therapy. If programming has been inappropriate, then programming changes can be made with a programming unit placed over the defibrillator site. Another important development has been the steady reduction in the energy required to terminate ventricular fibrillation. This reduction in defibrillatory threshold has been achieved by improvements in electrode design, use of the generator as an active electrode, and the use of biphasic configuration of the shocking wave. This in turn has led to the shift from sternotomy

approach with four leads and abdominal implantation to the present two-lead transvenous endocardial approach.

Current devices use anti-tachycardia pacing, and low- and high-energy shocks, known as tiered therapy. Devices recognise tachyarrhythmias by tachycardia cycle length, and can initiate the appropriate therapy. Anti-tachycardia pacing takes the form of adaptive burst pacing, with cycle length usually of that of the ventricular fibrillation. Should this fail, low energy shocks are given to terminate ventricular arrhythmia with the minimum of pain. These are then followed if necessary by high-energy shocks. With rapid tachycardias, the device can be programmed to give high-energy shocks as first-line therapy.

Further technological advances are likely and may include further reductions in defibrillator threshold, which will in turn increase the likelihood that a given shock will terminate ventricular arrhythmia, may shorten charge time by reducing the energy that has to be delivered, increase the life of the device and reduce the size of the device. Convergence of technology for defibrillation and for biventricular pacing may produce devices that can be used for both defibrillation and cardiac resynchronisation in patients with heart failure. Another technological development is the production of minimal feature devices suitable for prophylactic implantation only. These are likely to have cheaper initial costs owing to the reduced parameter set and shorter, less technical follow-up costs. After therapy has been delivered, the device would need to be replaced with a more advanced, fully featured device for secondary prevention.

Future-generation ICDs
Future-generation ICDs will likely become cardiac disease management devices. Sensors that can monitor the progression of heart failure and even follow intracellular and extracellular ion concentrations are under development. Devices that are currently in clinical investigations can monitor the extent of heart failure and potentially be developed to provide feedback management of heart failure by changing pacing rate, atrioventricular intervals, intervals in biventricular devices, or other parameters. Internet-based physician notification schemes or wireless communication from ICDs to nurses and physicians caring for patient may become reality and may drastically improve routine ICD (and pacemaker) monitoring of performance. In the meantime, routine ICD office checks remain the best method for monitoring devcei performance in individual patients. Other features such as ischaemic detection can potentially be incorporated in future-generations devices of ICDs.

Biophan Technologies, Inc. (West Henrietta, NY, USA) has recently issued two patents for methods of signalling the heart, which improve the function of implanted cardiovascular devices. The first patent is about a method of detecting and responding in a manner that avoids the onset of ventricular fibrillation. The method uses a low voltage electrical signal, which can be built into a low cost pacemaker and provide some protection against fibrillation events. The technology can also be deployed in ICDs as a means of controlling fibrillation to avoid the need for the more powerful and potential painful and disorienting 800 V charge traditionally used. Fibrillation of the heart often occurs when the electrical signals in the heart, normally somewhat chaotic and non-linear, become smooth and linear. Experiments showed that fibrillation could be avoided in a percentage of cases when a non-linear signal was applied to the heart (12;13). The patent teaches incorporating a circuit for detecting a change in the non-linearity of the heart's electrical signal that a pacemaker circuit is monitoring, and when the signal changes in a way that indicates the potential onset of fibrillation, the non-linear signal is sent to the heart. There are three benefits to this approach:

- This new technology can be readily integrated with existing ICDs,
- This may provide for a painless therapy option to complement existing anti-tachycardia pacing algorithms in today's ICDs,

- In addition, pacemakers that are predominantly used to prevent inappropriate slowing or stopping of the heart can be equipped with the ability to sense the pre-fibrillation phase that precedes sudden death and provide therapy using a low voltage pulse without requiring significant changes to existing low voltage pacemaker power design.

Some patients suffer anticipatory anxiety of an event that causes their defibrillator to fire. In Biophan's improved device design, the low voltage signal is applied first, before the more powerful 800 V jolt, to see if the fibrillation event can be avoided entirely. If not, after several attempts, the circuitry signals the more powerful and traditional cardioverter-defibrillator technology to trigger.

The second patent is about a high frequency pulse sequence in place of a single pacing signal so that stimulation of the heart can occur with lower energy, a technique with the potential to improve battery life of implantable devices.

Additionally, Biophan Technologies has issued a patent on providing nanomaterial-based biothermal power for ICDs and other implantable medical devices. Based on innovations in thermoelectric materials, this technology converts thermal energy produced naturally by the human body into usable electrical energy. The resulting power can be used to trickle charge batteries for devices with high discharge requirements, such as ICDs, or to directly power pacemakers.

D.3 Cardiac resynchronisation therapy devices

Cardiac resynchronisation therapy (CRT) can restore more-normal electrical contraction and, when combined with defibrillation, can have major impact on the mortality and morbidity of heart failure. CRT can reverse signs and symptoms of heart failure and in some patients improve ejection failure (14;15).

Most often the electrical signal to the left ventricle is delayed by the left bundle branch block, the right ventricle begins to contract a fraction of a second before the left ventricle instead of simultaneously. The result is an asynchronous contraction of both ventricles. This uncoordinated ventricular contraction further reduces the pumping efficiency of an already weakened heart muscle in cardiac heart failure patients. The electrical delay is visible on the ECG as widening of the QRS complex (above 120 to 130 ms) and helps to identify patients who might benefit from CRT. It should be noted, however, that there is today a general consensus that the QRS width is not precise enough to define the presence of mechanical ventricular dyssynchrony (16).

The idea behind CRT is simple: restoration of the normal coordinated pumping action of the ventricles caused by bundle branch block. CRT is administered via a pacemaker, called a CRT-P, or an ICD that has a built-in pacemaker, called a CRT-D. Common pacemakers are typically used to prevent symptoms associated with excessively slow heartbeats. CRT-Ps have three leads allowing simultaneous stimulation of the left and right ventricles and restore a coordinated, or synchronous pumping action. This is sometimes referred to as biventricular pacing. This reduces electrical delay and results in a narrower QRS complex on the ECG.

D.4 Complications and risks

A number of complications have been described with the use of ICD therapy. The most common complication is inappropriate ICD shocks that range from 21% to 25% (17;18). The most common cause of these shocks is atrial fibrillation, other supraventricular tachyarrhythmias, or sinus tachycardia. Although atrial fibrillation is not a contraindication to

ICD implantation, a careful assessment of heart rate during fibrillation should be performed to minimise the incidence of inappropriate shocks. Inappropriate shocks due to oversensing can also occur but are less frequent in current ICDs. Although, the effects of inappropriate shocks can be psychologically devastating in individual patients, in most cases, changes in ICD programming or adjustment of medical therapy can eliminate or decrease the incidence of inappropriate shocks. More serious complications can occur during and after implantation, such as pneumothorax, hemothorax, cardiac and pulmonary perforation, infection, lead dislodgment, thromboembolic events, haematomas and haemorrhage (17;19;20). Device failures include proarrhythmia (production of an iatrogenic arrhythmia), failure to detect an arrhythmia / inappropriate intervention, and lead fracture. Recently, a meta-analysis showed that battery abnormalities were the most common reported cause of device malfunctions for both pacemakers and ICDs (21).

Abbreviations

CRT   cardiac resynchronisation therapy
ECG   electrocardiogram
ICD   implantable cardioverter-defibrillator

Glossary

There are several types of arrhythmias:

Bradycardia

Bradycardia is a slow heart rate. The two most common causes of bradycardia are diseases of the sinoatrial node (heart's natural pacemaker), or other problems with the heart's electrical conduction system. Several therapies exist for bradycardia, including implantation of a pacemaker.

Tachycardia

Tachycardia is a fast heart rate. Sinus tachycardia results when the sinoatrial node sends electrical impulses faster than usual. Therapy includes implantation of an ICD.

Supraventricular tachycardia

Paroxysmal (starting and ending suddenly) supraventricular (originating above the ventricles) tachycardiais a series of fast atrial contractions that can cause the heart beat up to 250 times per minute.

Ventricular tachycardia

Ventricular tachycardia occurs when the ventricles produce impulses that make the heart beat too quickly. With this disorder, the heart tries to beat 200 or more times per minute. It cannot contract completely and just quivers. Ventricular tachycardia is treated with an ICD.

Fibrillation

Fibrillation is caused when the heart muscle begins to quiver, or fibrillate, continually and cannot contract normally. When a heart is in a state of fibrillation, there is no synchronisation between the atria and ventricles.

Atrial fibrillation

Atrial fibrillation is a very fast, uncontrolled atrial heart rate caused by rapidly fired signals. During an episode of atrial fibrillation, the atrial heart rate may exceed 350 beats per minute. Not all of these beats reach the ventricles, so the ventricular rate is not this high. However, the ventricular rate is often higher than normal and can also be erratic, exceeding 100 beats per minute. Sometimes an impulse will circle the atria, triggering atrial flutter.

Ventricular fibrillation

Ventricular fibrillation is a chaotic heart rate resulting from multiple areas of the ventricles attempting to control the heart's rhythm. Ventricular fibrillation can occur spontaneously (generally caused by heart disease) or when ventricular tachycardia has persisted too long. When the ventricles fibrillate, they cannot contact normally, hence, they cannot effectively pump blood. Ventricular fibrillation becomes more erratic, resulting in sudden cardiac arrest or sudden cardiac death. This arrhythmia must be corrected immediately via a shock from an ICD. The ICD can stop the chaotic electrical activity and restores normal heart rhythm.

D.5   References, websites

References

(1)   Bernstein AD, Camm AJ, Fletcher RD, Gold RD, Rickards AF, Smyth NP et al. The NASPE/BPEG generic pacemaker code for antibradyarrhythmia and adaptive-rate pacing and antitachyarrhythmia devices. Pacing Clin Electrophysiol 1987; 10(4 Pt 1):794-799.

(2)   Leung SK, Lau CP, Tang MO. Cardiac output is a sensitive indicator of difference in exercise performance between single and dual sensor pacemakers. Pacing Clin Electrophysiol 1998; 21(1 Pt 1):35-41.

(3)   Alt E, Combs W, Willhaus R, Condie C, Bambl E, Fotuhi P et al. A comparative study of activity and dual sensor: Activity and minute ventilation pacing responses to ascending and descending stairs. Pacing Clin Electrophysiol 1998; 21(10):1862-1868.

(4)   Toivonen L, Lommi J. Dependence of atrial sensing function on posture in a single-lead atrial triggered ventricular (VDD) pacemaker. Pacing Clin Electrophysiol 1996; 19(3):309-313.

(5)   Mond H, Stokes K, Helland J, Grigg L, Kertes P, Pate B et al. The porous titanium steroid eluting electrode: A double blind study assessing the stimulation threshold effects of steroid. Pacing Clin Electrophysiol 1988; 11(2):214-219.

(6)   Crossley GH, Reynolds D, Kay GN, Ferguson TB, Lamas G, Messenger J et al. Treatment of patients with prior exit block using a novel steroid-eluting active fixation lead. Model 4068 Investigators. Pacing Clin Electrophysiol 1994; 17(11 Pt 2):2042-2046.

(7)   Karpawich PP, Hakimi M, Arciniegas E, Cavitt DL. Improved chronic epicardial pacing in children: Steroid contribution to porous platinized electrodes. Pacing Clin Electrophysiol 1992; 15(8):1151-1157.

(8)   DiMarco JP. Implantable cardioverter-defibrillators. N Engl J Med 2003; 349(19):1836-1847.

(9)   Cannom DS, Prystowsky EN. The evolution of the implantable cardioverter defibrillator. Pacing Clin Electrophysiol 2004; 27(3):419-431.

(10)   Houghton T, Kaye GC. Implantable devices for treating tachyarrhythmias. BMJ 2003; 327(7410):333-336.

(11)   Maisel WH, Stevenson WG, Epstein LM. Changing trends in pacemaker and implantable cardioverter-defibrillator generator advisories. Pacing Clin Electrophysiol 2002; 25(12):1670-1678.

(12)   Garfinkel A, Spano ML, Ditto WL, Weiss JN. Controlling cardiac chaos. Science 1992; 257(5074):1230-1235.

(13)   Witkowski FX, Leon LJ, Penkoske PA, Giles WR, Spano ML, Ditto WL et al. Spatiotemporal evolution of ventricular fibrillation. Nature 1998; 392(6671):78-82.

(14)   Bradley DJ, Bradley EA, Baughman KL, Berger RD, Calkins H, Goodman SN et al. Cardiac resynchronization and death from progressive heart failure: A meta-analysis of randomized controlled trials. JAMA 2003; 289(6):730-740.

(15)   Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. N Engl J Med 2004; 350(21):2140-2150.

(16)   Kashani A, Barold SS. Significance of QRS complex duration in patients with heart failure. J Am Coll Cardiol 2005; 46(12):2183-2192.

(17)   Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. N Engl J Med 2002; 346(12):877-883.

(18)   Kadish A, Dyer A, Daubert JP, Quigg R, Estes NA, Anderson KP et al. Prophylactic defibrillator implantation in patients with nonischemic dilated cardiomyopathy. N Engl J Med 2004; 350(21):2151-2158.

(19)   Gradaus R, Block M, Brachmann J, Breithardt G, Huber HG, Jung W et al. Mortality, morbidity, and complications in 3344 patients with implantable cardioverter defibrillators: Results fron the German ICD Registry EURID. Pacing Clin Electrophysiol 2003; 26(7 Pt 1):1511-1518.

(20)   Kron J, Herre J, Renfroe EG, Rizo-Patron C, Raitt M, Halperin B et al. Lead- and device-related complications in the antiarrhythmics versus implantable defibrillators trial. Am Heart J 2001; 141(1):92-98.

(21)   Maisel WH. Pacemaker and ICD generator reliability: Meta-analysis of device registries. JAMA 2006; 295(16):1929-1934.

Websites
Biophan Technologies, Inc. (West Henrietta, NY, USA)
　　　www.biophan.com
Guidant Corporation (St. Paul, MN, USA)
　　　www.guidant.com
Medtronic, Inc. (Minneapolis, MN, USA)
　　　www.medtronic.com
St. Jude Medical, Inc. (St. Paul, MN, USA)
　　　www.sjm.com
Vitatron BV (Arnhem, The Netherlands)
　　　www.vitatron.com

Appendix E: Telemedicine

E.1 Definition

Telemedicine has been defined by Wootton as health care at a distance (Wootton & Craig, 1999). The American Telemedicine Association describes it as "The use of medical information exchanged from one site to another via electronic communication for the health and education of the patient or health care provider and for the purpose of improving patient care". The following, by the World Health Organisation, is more simple and clear: "Telemedicine is the practice of medical care using interactive audio visual and data communications. This includes the delivery of medical care, diagnosis, consultation and treatment, as well as health education and the transfer of medical data." Telemedicine is essentially doctor-to-doctor, with the patient somewhere in the system, and typically involves consultations with specialists at a distance.
In essence, it is thus the use of information and communication technologies (ICT) to support health care delivery. It is efficient in cases where expert advice is available from a distance, but not locally.

A number of closely related concepts and terms are also being used. Telecare has been defined as "the continuous, automatic and remote monitoring of real time emergencies and lifestyle changes over time in order to manage the risks associated with independent living." To elaborate the meaning, devices range from those where the user presses a button that raises an alert at a control centre, to systems that monitor the person's well-being and/or environment and which trigger (without, if necessary, conscious involvement) a warning that the person's well-being has deteriorated, or that an untoward event has occurred. Some systems give the person immediate feedback so that memory problems in particular can be accommodated and the person's dignity and independence maintained. In all cases except the latter, procedures for delivering an appropriate response from an external person (carer, neighbour or statutory service, etc.) are vital to the whole system.
http://www.telecareaware.com/what-is-telecare/
Telehealth / telemonitoring is "the remote exchange of physiological data between a patient at home and medical staff at hospital to assist in diagnosis and monitoring". It includes (amongst other things) a home unit to measure and monitor temperature, blood pressure and other vital signs for clinical review at a remote location (for example, a hospital site) using phone lines or wireless technology. Examples of telehealth devices are blood pressure monitoring, blood glucose monitoring, cardiac arrhythmia monitoring and medication reminder systems. http://www.telecareaware.com/what-is-telecare/

Telemetry is the transmission of data captured by instrumentation and measuring devices to a remote station where it is recorded and analyzed. Wireless medical telemetry has been defined as: "the measurement and recording of physiological parameters and other patient-related information via radiated bi- or unidirectional electromagnetic signals". Biotelemetry comprises telemetry applied to medical, human research, animal and implantable fields.

Furthermore, there appear to be almost as many branches of medical 'tele-s' as there are medical specializations. Best known are teleradiology, teleultrasound, teledermatology, telecardiology, telesurgery and telepathology.

Finally, the term which covers the broadest field is probably eHealth. This term was introduced in 2000, but has spread widely since. It has become an accepted term, even though there is no clear consensus on the definition. A systematic surveys came to a total of 51 unique definitions in scientific literature covering a wide range of themes without clear consensus (Oh et al 2005a, Oh et al 2005b). Two universal themes were identified to be health and technology. In addition, six less general themes were also found: commerce, activities, stakeholders, outcomes, place and perspectives. In a related article, Pagliari et al (2005) pose that the field may best be characterised by two global definitions: "e-health is the use of emerging information and communication technology, especially the Internet, to improve or enable health and healthcare" (Eng 2004) and "e-health is an emerging field in the intersection of medical informatics, public health and business, referring to health services and information delivered or enhanced through the Internet and related technologies. In a broader sense, the term characterizes not only a technical development, but also a state-of-mind, a way of thinking, an attitude, and a commitment for networked, global thinking, to improve health care locally, regionally, and worldwide by using information and communication technology" (Eysenbach 2001). It is important to realize that most of the definitions specify the use of networked digital technologies, primarily the Internet. The European Commission states that "e-Health refers to the use of modern information and communication technologies to meet needs of citizens, patients, healthcare professionals, healthcare providers, as well as policy makers" and that "e-Health is today's tool for substantial productivity gains, while providing tomorrow's instrument for restructured, citizen-centred health care systems and, at the same time, respecting the diversity of Europe's multi-cultural, multi-lingual health care traditions. There are many examples of successful e-Health developments including health information networks, electronic health records, telemedicine services, wearable and portable monitoring systems, and health portals." http://europa.eu.int/information_society/eeurope/2005/all_about/ehealth/index_en.htm In the future, many more applications can be expected.

In this Chapter, we will use some but not all of the above terms. Where multiple terms are applicable, we will use the term telemedicine.

E.2 Overview

In one way or an other, all telemedical applications use ICT. Over the past decade, computers and ICT have become increasingly accessible and cost-effective as a means of providing educational and health care services (Telerehabilitation Position Paper, 2005). This has occurred simultaneously with an increased emphasis on the quality of rural health care services, a focus on evidence-based outcomes, and a general increase in demand on practitioners' time and expertise. In principle, telemedicine is not new. Telemedicine can be as simple as a telephone interview, possibly supported by a videolink, faxing or e-mailing X-rays, ECG's, or other investigation results, or sending samples to a consulting physician or medical laboratory. Of great importance for modern telemedicine applications, however, are the increasing possibilities for wireless communication.
The innovations which are enabled by the above mentioned developments are the main reason why telemedicine is expected to have a rapidly increasing impact on a very broad spectre of medical technologies and why it was included in this report.

In main terms, telemedicine and telecare have the following benefits (McLaren, 2003):
- Improved access to information
- Provision of care not previously deliverable
- Improved access to services and increasing care delivery
- Improved professional education
- Reduced health care costs
- Improved knowledge about clinical communication

Based on these main terms, reasons to use telemedicine can be that it is the only alternative in remote or rural areas, on board ships and planes or on the battlefield. Furthermore, it can be better because it provides access to the best specialists in a much shorter timeframe. Finally, if the appropriate technology is used, i.e. not unnecessarily complex, it can also be less expensive. For example, a study carried out more than 5 years ago, when broadband internet was still quite expensive, showed that low-cost, low-bandwidth PC-based telemedicine consultations provided a very useful support in rural health care (Norris, 2002). Also for the increasing number of elderly patients telemedical methods may provide a means of access to optimized and cost-effective healthcare (Jürgens and Tost, 2006).

E.2.1 ICT

ICT has an innovation capacity that may be useful within different areas of social services (Beckers et al, 2005)). This innovation capacity displays itself in three ways:
1. Innovation of processes: making processes more efficient
2. Organizational innovation: re-organizing processes
3. Institutional innovation: development of new drafts and projects

Developments in ICT do have much influence in everyday life. In this context ICT is also called 'ambient technology'. The main macrotechnological developments are summarized below:
- Integration/ fusion of infrastructures and applications
- Multimedial applications (more and more multi-purpose appliances are used)
- Unwiring and 'mobility'
- Broad band (the band width of particularly (glass fibre) cable technology has increased enormously)
- Geographic information systems (development of GPS)
- Miniaturization and reflectiveness (In domotica the increased convenient use is very important)
- Detection technology (ICT is becoming more a monitoring and detection tool; e.g. the combination of webcam and internet)

These same developments can also be used to the advantage of medical applications. Especially for telemedicine and telehealth, the availability in everyday life in hospitals as well as in private homes allows the easy integration of medical care at a distance.

E.2.2 Wireless communication

Advances in wireless technology are opening up an ever increasing field of opportunities for cost reduction, increased patient safety, better data collection and increased convenience for practioners and patients (Traherne et al., 2005). Several slightly different systems exist.
One of the most popular wireless standards for communication is wireless LAN, sometimes called WiFi or IEEE 802.11. Developed originally for mobile or nomadic computer users, it is now being added to portable devices and cordless and mobile phones. It can deliver high data rates of up to 52 Mbit/s using a shared, unlicensed radio band at 2.4 GHz. Many medical instruments nowadays include a wireless LAN interface, or a slot where one can be plugged

in, to deliver data to hospital IT systems or portable computing devices, and this trend will continue with equipment intended for professional use.

Another technology that has grown spectacularly is Bluetooth, which uses the same 2.4 GHz unlicensed band as wireless LAN. It is designed to operate over a short range: up to approximately 100 m and to support a small number of devices networked together in piconets of up to eight devices. This means that the whole radio or the whole instrument can be put onto a single chip. It is also a relatively low-power technology, with eight hours of continuous operation from a single charge of a battery weighing 20 g. Because Bluetooth is already available in cell phones, a vital-signs monitor can send regular updates via the phone from a patient in the field.

ZigBee (www.ngbee.otg) is a new local area radio standard that is gaining rapidly in popularity. It uses the 2.4 GHz unlicensed band, as well as the 902 MHz band in the US and the 868 MHz band in Europe. ZigBee is intended for battery-operated devices that only send small amounts of data; it is designed so that a battery could last for many years, if necessary. This could be ideal, especially at home or in a small clinic, for an electronic thermometer or a sphygmomanometer which links to a data-collection unit.

Digital Enhanced Cordless Telecommunications (DECT) is a standard for cordless telecommunications with an exclusive band. This inexpensive system is designed to offer a high quality of service to an application that sends and receives a continuous stream of data. The used band is exclusive and it is free from interference from other systems.

Near-field communication is a recent development of radio-tagging technology, which allows medium data rates (100 kbit/s and more) over a range of a few centimetres. This relatively simply to use technique not even requires a battery for some applications.

Proprietary radios remain common in the medical arena for a number of reasons. The main reason is, that sometimes no standard system is suitable for a particular application. This technique can use any band available, dedicated or not.

The next big innovation in the development of faster wireless communication is going to be the control over terahertz waves, or T-rays, which sit on the electromagnetic spectrum between infrared and microwaves (Graham-Rowe, 2006).

The UHF frequency bands used by wireless medical telemetry are getting crowded. More and more competing users are occupying those frequencies, putting medical telemetry at an ever greater risk for harmful interference. On June 12, 2000, the Federal Communications Commission (FCC) in the United States released a report and order (FCC No. 00-211) making new frequencies available for medical telemetry use on a primary basis. This will allow medical telemetry to be protected from other radio transmissions in the same band. The special frequency bands allocated by FCC are called the Wireless Medical Telemetry Service (WMTS).

More features of these wireless technologies are summarized in table E.1.

E.2.3 Examples of telemedicine applications

Due to the vast and rapidly increasing number of telemedicine applications which are already in clinical use or under development, this section includes only a brief description of a selection of telemedicine applications.

Telemedicine involves the transmission of data over distance (McLaren, 2003). Often this has been between units providing health care but increasingly it is being used to link the health care provider with the patient's home. In conventional consultations, the physician applies the senses of sight, sound, smell and touch to make a diagnosis and to decide on a treatment plan.

In telemedicine, the input is limited to sight and sound, although rudimentary electronic 'noses' have been developed.
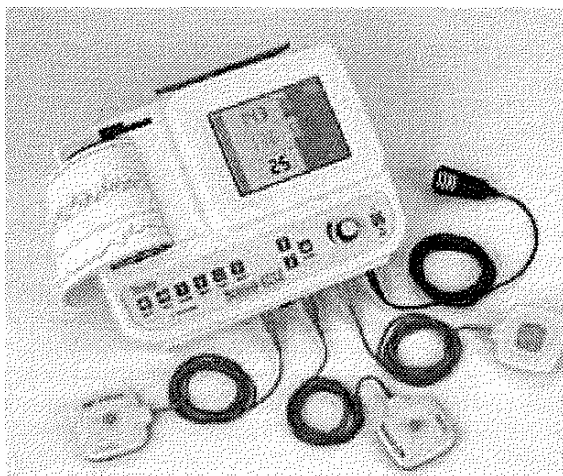
An example with a potentially great impact is the introduction of Electronic Medical Records (EMR) for patients. Ideally, an EMR would contain all patient information, including personal information, medical history, medical images, associated reports and other relevant health information. Every physician could obtain immediate access to all relevant data for his patients using the EMR, which would lead to faster diagnosis, avoiding incidents with e.g, incompatible combinations of medications or allergies and improved patient care. A pilot trial was started in the Netherlands in 2004.

Ambulatory telemetry systems allow patients to move around the hospital while certain physiologic parameters are monitored (Health devices 31, 2002). Traditionally, telemetry systems have used compact transmitters worn by the patient to take readings and transmit them to a central station. More recently, to expand telemetry's capabilities without adding excessive size and weight to the patient-worn transmitters, some suppliers have provided certain parameters using wireless portable bedside monitors that are wheeled around on a roll stand by the patient.
An example of a specific application is the use for patients who are at risk of abnormal heart activity, generally in a coronary care unit. Such patients are outfitted with measuring, recording and transmitting devices. A data log can be useful in diagnosis of the patient's condition by doctors. An alerting function can summon nurses if the patient is suffering from an acute or dangerous condition.

Pacemakers and ICD devices have become available with telemetry features that can be used at home. Devices can be programmed to perform daily device and physiologic data checks initiating an alert if a problem is detected, even while the patient is asleep. Furthermore, also updates of the programming can be performed fast, non-invasive and efficient by the wireless connection. http://www.medtronic.com/physician/conexus/

Another example of telemetry is shown with fetal monitors that detect, display, and print a record of fetal heart rate (FHR) with telemetry capabilities (ECRI, 2004). Fetal monitors detect FHR externally by using an ultrasound transducer to transmit and receive ultrasonic waves. The frequency (or Doppler) shift of the reflected signal is proportional to the velocity of the reflecting structure; in this case, the fetal heart. Some units have external or internal telemetry systems in which the FHR and internal uterine activity (UA) signals are transmitted by radio waves to a receiver at the fetal monitor. During continuous monitoring, the mother wears a pocket-sized transmitter, allowing her to walk around between contractions. FHR and UA data can also be transmitted to a medical institution remotely over telephone lines.

Figure E.1: Example of a home FHR monitor

Mass community screening for diabetic retinopathy is performed using a non-mydriatic camera with telemedicine (Boucher et al., 2005). Diabetic retinopathy is a leading cause of blindness. Studies have shown the value of screening and early, timely treatment. In this prospective, population-based cross-sectional study, diabetics recruited through a regional multimedia campaign were surveyed and screened. Pictures of the eye were originally saved on the local harddisc in TIF format and transmitted at the end of the day to the hospital server, with lossless compression through the FTP transfer protocol on the Quebec sociosanitary transmission network (RTSS) with a 256 kbit/s internet connection. The outcome of the study: Telemedicine provided a reliable and highly acceptable method for diabetic retinopathy screening. It can attract a significant number of people with diabetes and potentially recruit patients who would otherwise be missed by the current methods of vision screening.

In acute stroke care, rapid but careful evaluation of patients is mandatory but requires an experienced stroke neurologist. Telemedicine offers the possibility of bringing such expertise quickly to more patients. Handschu et al. (2003) tested for the first time whether remote video examination is feasible and reliable when applied in emergency stroke care using the National Institutes of Health Stroke Scale (NIHSS) (see Figure E.2). They used a novel multimedia telesupport system for transfer of real-time video sequences and audio data. The remote examiner could direct the set-top camera and zoom from distant overviews to close-ups from the personal computer in his office. Acute stroke patients admitted to the stroke unit were examined on admission in the emergency room. Standardized examination was performed by use of the NIHSS (German version) via telemedicine and compared with bedside application.
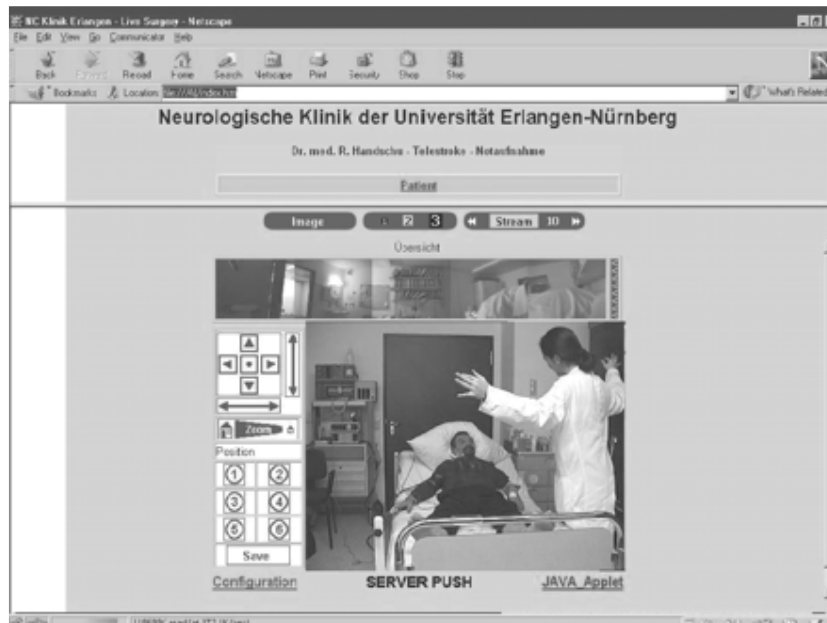

Figure E.2: Example of video examination seen at a desktop-PC

A promising opportunity for saving time is bringing expertise to patients treated in smaller hospitals by linking hospitals together with the use of telemedicine. This technology may reduce transfer of patients and associated adverse events. The needs for telemedicine in stroke medicine were described clearly by Levine and Gorman in 1999. They named the mandatory elements of a telestroke system: transfer of imaging data and a review of clinical findings

viewable at a remote computer workstation. For imaging data, fairly good systems using Digital Image and Communications in Medicine (DICOM) standards are now available and in use. To perform clinical examination while linked to academic centres, real-time transmission of video and audio sequences with high speed data connections is necessary. The conclusion was that remote examination of acute stroke patients with a computer-based telesupport system is feasible and reliable when applied in the emergency room.

E.3   Risks and hurdles for innovation

In main terms, telemedicine has the following drawbacks (McLaren, 2003; Hjelm, 2005):
-    Compromised relationship between health professional and patient
-    Compromised relationship between health professionals
-    Issues of the quality of clinical information
-    The need for major organisational changes in the way that health care is provided, to maximise its potential

In addition to the last issue, the reimbursement system has been identified as a crucial factor for the success of telemedicine. If this has not been regulated, then an efficient use of the benefits of telemedicine is severely hampered (Kumar, 2005). Furthermore, patient privacy could be jeopardised if the protection of data has not been secured. Regional or national privacy regulations might also provide hurdles, for example when electronic patient records are used. The use of the Internet, as most specifically mentioned in the concept of eHealth, obviously adds to the concerns of patient privacy. Internet hackers have already proved that it is possible get access to such systems.

Probably the most important risk of telemedicine is related to errors in data transmission, leading for example missed alarms or to false diagnoses and subsequent inadequate or falsely indicated treatment. Errors can be related to any kind of system failure, however, the largest recognised source of errors is electromagnetic interference in wireless communications (see below). Given the expected further increase of applications using some kind of telemedicine or eHealth aspect, it is important that risks are managed at a European level. Actions to coordinate this have been initiated by the European Commission.

The three main security hazards for wireless communication are (Slagter et al., 2003):
-    Eavesdropping (Unauthorized people try to listen in on the communication about patient information)
-    Injecting messages (Unauthorized people try to modify patient information)
-    Removing messages (people try to scramble a radio signal to prevent communication)

A well recognized risk is the risk of electromagnetic interference with other wireless devices such as telephones, laptops, palmtops or other medical devices. As explained in paragraph E.2.2, an example of risk control is the WMTS system in the US. The Medical Implant Communications Service (MICS) radio frequency band, was designated worldwide for medical devices. Very recently, the FDA has issued a draft guidance document (for comments) on radio-frequency wireless technology in medical devices. This document addresses issues and concerns pertinent to the safe and effective use of such technology and also provides guidance with regard to risk management options and an overview of relevant standards and telecom information. (http://www.fda.gov/cdrh/osel/guidance/1618.pdf).

In Table E.1, the disadvantages of the different available wireless systems are summarised.

Table E.1: disadvantages of wireless systems (Traherne et al., 2005)

System	disadvantages
Wireless LAN (802.11)	- Poor at real time data - Requires relatively high power, so unsuitable for small battery-powered applications - Does not scale-up well to large numbers of users in a given space
Bluetooth	- Requires relatively high power (but less than wireless LAN), so unsuitable for extremely small battery-powered applications - Untethered instrument head - Short range, typically 10 m maximum
DECT	- No band in US (although can use 2.4GHz) - Relatively low data rate
ZigBee	- Low data rate - Limited mobility so far
Near-field communications	- Short range (few cm) - Still in development
Proprietary	- Costly and risky to design a complete radio system (but can mitigate by adapting a standard system)

Specific drawbacks concerning the use of fetal heart rate monitors (FHR) are the following:
- Some investigators have expressed their concern about the possible risks associated with fetal exposure to ultrasound. These risks have not been clearly defined.
- Sensor positioning may be difficult, since the fetus is not visible.
- One of the most common problems associated with telemetry is signal fading, during which the signal is momentarily lost. This can result in inaccurate signals, false alarms and loss of monitoring data.

A number of problems was identified for the use of telemetry for mass community screening for diabetic retinopathy:
- 18% of the patients felt that a standard eye examination with an ophthalmologist was irreplaceable because they believed in the importance of personal interaction with an eye care professional. (Compare with main term drawback of telemedicine)
- A small fraction of the patients (3.2%) admitted they did not trust the technology and questioned the validity of the camera.

Several ambulatory telemetry systems have been evaluated and cannot be recommended:
- Criticare MPT. MPT is the world's first monitor that can be worn by a patient and monitor the patient's ECG, blood pressure, heart rate and oxygen level. It also offers the capability of two-way communication. Multiple patients can be monitored from a single viewing station. That same station can send a signal to the patient's bed, instructing the patient-borne monitor to take a specific reading. However, it has one of the largest and heaviest transmitters and it has the shortest battery operating time.
- Life Sensing Instrument TeleTrens: operates in the VHF frequency band (interference with local tv broadcast)

Points against Telemedicine in emergency evaluation of acute stroke:
- To provide additional information about imaging or text and laboratory data, the multimedia system used in this study could also handle other data sources like DICOM data or HTTP connections via a computer network and thus could be the cornerstone of a larger telestroke network. It also seems to provide better video quality and remote-control mechanism but requires quite higher bandwidth compared with standard videoconferencing systems.

-       Before telemedicine will reach more widespread use in stroke care, technology should be
        optimized, especially with regard to data compression algorithm and data speed.
        Moreover, there are some basics like light, background, and acoustics in the examination
        room that need to be addressed when a telemedicine service is begun. For examination of
        patients lying on a hospital bed, which is most suitable in acute care, optimal camera
        position and angle are necessary. Subsequently, the size and shape of the examination
        room must be taken into account. Finally, a clear description and high grade of
        standardization of the whole process are crucial, and bedside assistants must receive
        good training.

Finally, an important hurdle in the application of telemedicine service can be the
incompatibility of hardware and software systems. It can occur that equipment will only
communicate correctly if all components come from the same manufacturer. For example,
transmission of physiological signals such as EKG, EEG, EOG and EMG have generally only
been possible between equipment made by the same manufacturer. The IEEE's ISO/ IEEE
11073-10201 and the File Exchange Format for Vital Signs hope to allow standardisation.

E.4   References

McLaren; Advances in Psychiatric Treatment (2003), vol. 9, 54–61.
Beckers et al.; Arbeidsproductiviteit in de zorgsector en ICT (2005): Center for public
    innovation, Rotterdam.
Boucher MC et al.; Mass community screening for diabetic retinopathy using a nonmydriatic
    camera with telemedicine; Can J Ophthalmol (2005); vol.40,734-742.
ECRI (2003): Healthcare Product Comparison System, April 2003.
ECRI (2004): Healthcare Product Comparison System, June 2004.
Eng TR. Population helath technologies: emerging innovations for the health of the public.
    Am. J. Prev. Med. (2004); 26: 237-242.
Eysenbach G. What is eHealth?) J. Med. Internet Res. (2001); 3:e20.
Graham-Rowe D. Taming the Terahertz. MIT Technology Review, November 30, 2006.
Handschu R et al.; Telemedicine in emergency evaluation of acute stroke; Stroke (2003); 34,
    2842-2846.
Health devices 31 (9), 2002.
Hjelm, NM; Benefits and drawbacks of telemedicine; J Telemed Telecare (2005); vol.11, 60-
    70.
Jürgens C, Tost F. Fortschritte in der geriatrischen Betreuung durch Telemedizin.
    Ophthalmologe (2006); 103: 749-754.
Kumar S, Constable IJ, Yogesan K, Reimbursement for internet based eye care. Br. J.
    Ophthalmol. (2005); 89: 1234-1235.
Norris TE, et al. Low-bandwidth, low-cost telemedicine consultations in rural family
    practice. J. Am. Board Fam. Pract. (2002); 15: 123-127.
Oh H, Rizo C, Enkin M, Jadad A. What is eHealth?: a systematic review of published
    definitions. World Hosp. Health Serv. (2005); 41: 32-40.
Oh H, Rizo C, Enkin M, Jadad A. What is eHealth (3): a systematic review of published
    definitions. J. Med. Internet Res. (2005); 7: e1.
Pagliari C, Sloan D, Gregor P, et al. What is eHealth (4): a scoping exercise to map the field.
    J. Med. Internet Res. (2005); 7: e4.
Slagter et al.; Architecture requirements for a healthcare application (2003): Telematica
    Instituut, UT

Telerehabilitation Position Paper (2005): The American Occupational Therapy Association
Traherne et al.; Wireless technologies in health care (2005), Medical device technology january/february 2005
Wootton, R. & Craig, J. (eds) (1999) Introduction to Telemedicine. London: Royal Society of Medicine Press

Appendix F   Advanced home care technology

F.1   Definition

Introduction of new medical technology primarily takes place in (academic) hospitals. After several years of experience and adaptation, some technologies are introduced in other settings such as the patients' home. Consequently, most of the complex medical technology used in homecare is initially not developed to be used at home (Vondeling e.a., 1996). Over the years those 'advanced home care technologies' are finding increasing use. Budgetary considerations and the widespread wish to receive care at home are some reasons behind this growth.

The growing use of medical devices in less controlled environments, like the patients' home, may imply (new) risks. Therefore, the use and risks of advanced home care technology were studied by the National Institute for Public Health and the Environment (Hollestelle et al., 2005). Results of this Dutch study are briefly described in this paragraph.

F.2   Overview

Home care technology covers medical devices for treatment and nursing by professional carers at home or by patients and informal carers under the responsibility of professionals (Quak, 2003).

Such medical devices may be used to support physiological functions, to administer substances and patient monitoring. Examples of each category are shown in Textbox F.1. In vitro diagnostic devices used at home (e.g. glucose meters) were beyond the scope of the study.

Textbox F.1: Examples of advanced medical technology used in home care

a. Devices supporting physiological functions:
- Ventilators
- Continuous positive airway pressure (CPAP)-machines
- Powered suction pumps
- Oxygen delivery devices
- Dialysers
- Electrical pumps used for negative pressure wound therapy
- Alternating pressure mattresses for the prevention of decubitus
- Transcutaneous Electrical Nerve Stimulators
- Continuous Passive Motion (CPM) devices to aid recovery after joint surgery
- Home traction devices

b. Substance delivery devices:
- Infusion pumps for delivery of medication and blood
- Insulin pumps
- Infusion pumps for total parenteral nutrition (TPN)
- Enteral feeding devices
- UV-therapy devices
- Nebulizers

c. Patient monitoring devices:
- Fetal monitoring devices
- Respiratory and circulatory monitoring devices (e.g. pulse oximeter)

Home care technologies sometimes have fewer features than the hospital equivalent. Many technologies also come as portable versions, creating more freedom of movement for the patient. Besides, some home care devices already have remote patient monitoring possibilities. An example is the nocturnal home haemodialysis where the alarm signals and readings of a dialyser can be monitored at a remote site.

Several advanced home care technologies are already used frequently in the Netherlands, e.g. nebulizers, oxygen delivering devices, infusion pumps, Transcutaneous Electrical Nerve Stimulators, and CPAP-machines. Other technologies, for example electrical pumps used for wound therapy, are not yet widely used as they are the subject of research projects or because of difficulties in organizing the home care.

Over the last few years, Dutch figures show an increase in the use of most advanced home care technologies. Given the growth of chronically ill patients (COPD, diabetes) in the near future and the ageing population (Telemedicine Alliance, 2004; WHO, 2005) it is expected that the application of these technologies will continue to expand.

F.3   Possible risks

Home use of complex medical devices implies several risks. The highest risks are found in the use of invasive technologies (e.g. enteral feeding devices, powered suction pumps), life-supporting technologies (e.g. ventilators) or substance delivery devices (e.g. infusion pumps). Risks of advanced home care technology are mainly related to use errors. Examples are incorrect storage, cleaning and maintenance of the device, erroneous programming, depleted batteries or misinterpretation of alarms. Besides, failures in design and technical problems (breakdown, alarm failure) may also occur. A new type of risk is technical problems when sending data to the hospital in distance patient monitoring.

Many of these risks are not specifically related to use of the device at home, but these risks may be increased due to several factors:
-    Various parties are involved in technology-enhanced home care (e.g. hospital, home care organisation, medical equipment providers). This may increase the risk of transfer errors or unclear responsibilities with regard to instructions, maintenance of the equipment, etc.;
-    Home treatment may be too much of a burden to formal and informal carers, in particular when patients are treated with multiple devices (for example total parenteral nutrition with an infusion pump in combination with oxygen therapy);
-    Devices that were initially developed for hospital use may be too complicated for use at home. In addition, instructions for use may not be written for use of these devices at home;
-    Compared to hospital staff, general home care providers generally have less expertise in operating advanced medical devices;
-    Supervision of device programming by a second care provider is often not possible when a device is used at home;
-    Technical procedures of the caregiver may be disturbed (e.g. by intake of new patients by phone) and ergonomic circumstances at the patients home may not be optimal (e.g. space, light);
-    At home device monitoring possibilities are limited. Therefore, medication or programming errors may be discovered after some time and may cause more patient harm;

-   The patient and the informal carer, who will also operate the device, lack professional knowledge and skills;
-   At home there are several factors that may disturb the functioning of the device (e.g. children, electricity facilities, heaters);
-   Technical failures may be discovered at a later point of time. Besides, replacement of defective devices may take longer than in an intramural care setting;
-   In homecare cleaning, maintenance and calibration of medical devices are not always clearly arranged.

In conclusion, to enhance patient safety it is of importance that advanced home care devices are designed for use at home and have clear instructions for use. Organizational precautions that can be taken are employment of specialized nursing teams and a clear demarcation of tasks and responsibilities of all parties that are involved in home care technology. Finally, instruction and monitoring of patients and informal carers must be part of technology enhanced-treatments.

F.4   References

Hollestelle ML, Hilbers ESM, Tienhoven EAE, Geertsma RE (2005). Overview, frequency of use and risks of advanced medical technologies in home care.

Quak ABWM, Bruin SR de, Beekum WT van. 2003. Inleiding tot de thuiszorgtechnologie. In: Handboek zorg thuis. Maarssen: Elsevier Gezondheidszorg. C 5.1-1 – C 5.1-24.

Telemedicine Alliance (EESA, WHO, ITU) (2004). Telemedicine 2010: Visions for a personal medical network.

Vondeling, H, Rosendal, H, & Banta, HD. Diffusion of medical lasers in the Netherlands. In: Knowledge, technology transfer and foresight (1996) . Inzelt, A. & Coenen, R. (red). NATO ASI series 4, Science and Technology Policy, vol. 8, pp. 73-98. Kluwer Academic Publishers, Dordrecht.

WHO (2005). Chronic diseases and health promotion. Impact of Chronic disease in Europe. http:www.who.int/chp/chronic_disease_report/en/ http:www.who.int/chp/chronic_disease_report/media/impact/Netherlands.pdf