Medical Technology

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Medical Technology – Meeting Tomorrow's Health Care Challenges

John Grue and Anne-Brit Kolstø (eds.)

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Preface with summaries of the chapters

This volume contains the written versions of the talks presented at a symposium with title: "Medical Technology – Meeting Tomorrow's Health Care Challenges", organised jointly by the Norwegian Academy of Science and Letters (DNVA) (www.dnva.no), the Norwegian Academy of Technological Sciences (NTVA) (www.ntva.no) and the Research Council of Norway (RCN) (www.rcn.no). The symposium was held in the House of the Academy (DNVA) in Oslo on 29th January, 2014 and had 165 participants.

Bent Høie, Minister of Health and Care Services, gave the introductory talk. Experts invited by the learned societies then presented talks on: Technical medicine in tomorrow's health care; Innovation for health in developing countries; From basic research to innovation; Technology both strengthens and challenges health care.

The following participants contributed by discussion and comments to the talks: Øivind Røise (Oslo Municipality), Petter Planke (Redcord AS), Kjell Borthne (Ahus), Per Johan Lysberg (Siemens Healthcare Diagnostics AS), Kathrine Myhre (Oslo Medtech), Anne Spurkland (University of Oslo), Stein Evensen (University of Oslo), Helge Kildal (Consultant) and Kristin Braa (University of Oslo).

Together, DNVA and NTVA represent the entire spectrum of the learned disciplines. RCN is the Government's adviser on science issues. By the organisation of an annual symposium series like this, focusing on a subject of high political priority, the two academies and RCN want to develop this kind of science communication.

Previous symposia in the series – and book publications with the same titles: Marine Transport in the High North, held on 19th October, 2010; Norwegian Energy Policy in Context of the Global Energy Situation, held

on 1st February, 2012; Food from the Ocean – Norway's Opportunities, held on 30th January, 2013.

The scientific committee of this year's Symposium: Executive Director Anne Kjersti Fahlvik (RCN), Professor Roy H. Gabrielsen (University of Oslo), Professor John Grue (University of Oslo), Professor Anne-Brit Kolstø (University of Oslo) and Professor Anne Spurkland (University of Oslo).

We acknowledge with gratitude the assistance by Mr. Adrian Read, acting as Editorial Assistant of this publication, and Mr. Eirik Lislerud of DNVA for taking on the practical matters with the organisation of the Symposium. The Symposium was jointly funded by DNVA, NTVA and RCN.

Short summaries of the chapters of this Volume:

In Chapter 1, Bent Høie, Minister of Health and Care Services, writes that the Government's ambition is to build a health service for the patients, which will also mean better and safer health care. Technological developments such as health apps give new opportunities. The Government has stated in the Sundvolden Platform that medical research should be strengthened, especially regarding serious diseases and the prevention of lifestyle diseases. There will be strong focus on innovation, research and technological developments. ICT and eHealth are important tools to achieve better health and a state of the art health and care service.

The Minister has high expectations for the outcome of the HelseCare21-strategy, the first national multisectorial strategy for research, development and innovation for the health and care services. New technology to the benefit of patients should be safe, improve the results of treatment and should also be cost effective. New technologies should support health care personnel and at the same time increase the efficiency of their time and resources.

Høie believes that digitalisation provides an opportunity to empower patients, and that digitalisation is needed to create patient-centred treatment where citizens can take charge of their own health care services. ICT in the health and care sector is one of eight high-priority issues in the Ministry of Health and Care Services. Patient records should be digital. The data should

be available for quality improvement, health monitoring, management and research. The Government will promote a National Health and Hospitals Plan to enable a new, smarter, and better management of the hospitals, as well as ensure clear roles and task sharing across the health sector.

In Chapter 2, Kristin Braa, Petter Nielsen and Ola Titlestad of the University of Oslo discuss mobile technology for health care (mHealth) – an emerging research area – in developing countries, with projects in Africa particularly emphasised. With its access in regions where other infrastructure is often lacking, mobile technology offers a particular opportunity to collect, communicate and co-ordinate health data.

The Health Information Systems Programme (HISP) is a global network established to strengthen health information systems in developing countries. Managed and co-ordinated by the Department of Informatics at the University of Oslo, HISP has developed the District Health Information Software DHIS 2. This is an open-source based software (no licence required) and offers support for health sector reforms towards decentralisation and the development of health districts.

While the strategy of HISP is to build on the existing installed base of information systems, DHIS 2 enables integration of the vertical flow of data from various health programmes at district level. DHIS 2 facilitates collection, validation, analysis and presentation of aggregate statistical data used for health information management activities. DHIS 2 is designed to administrate a broad range of integration scenarios. It is used in many countries as a central data warehouse. Data can be submitted via SMS, Java applications, by mobile phone browser, Android App, or by PC/laptop/tablet.

Three core challenges motivate the HISP initiative: 1) there are substantial differences in the access to infrastructures and human resources and in particular between urban and rural areas; 2) health information systems in developing countries are struggling with fragmentation as a result of multiple parallel systems; 3) there is a critical lack of competence related to health information itself and systems of its support. DHIS 2 is gradually becoming a global standard. A list of recommendations relevant also outside HISP is given.

DHIS 2 was awarded the Innovation Prize of the University of Oslo in 2013.

In Chapter 3, Jan Terje Andersen, Ole Kristian Hjelstuen and Inger Sandlie of the University of Oslo discuss two issues: innovative basic research in molecular biology, and the application of the results to make new products in the pharmaceutical industry. They explain how their findings, combined with knowledge generated by others, may revolutionise the way we take medication, dramatically increasing the time lapse between each dose of a drug, as well as reducing the dosage needed.

The first part explains the importance of some older data and a hypothesis that had been generated in another country, and with other scientific questions in mind. The authors describe how their own curiosity-driven research was triggered by this earlier knowledge and the follow-up results published from other laboratories.

Andersen and Sandlie showed that both one of the major classes of the human defence molecules against infections, immunoglobulin IgG, and the transport molecule in the blood, albumin, can bind to the same receptor molecule, at the same time. The binding to this receptor molecule protects both the immunoglobulin molecule IgG and albumin against rapid turnover, and allows the molecules to circulate in the blood for a longer period.

In the second part, industry co-operation and commercialisation strategies are discussed. The company Novozymes A/S was already working with the production of albumin and had patented technology for the binding of drugs to albumin, and they contacted the Sandlie group to obtain collaboration. Sandlie and her co-workers designed new albumin variants that could increase the half-life of the albumin in the blood, as well as the drugs bound to the albumin.

Commercialisation strategies are discussed, and it is explained why the best solution for the Sandlie research group was to enter into agreements with an existing company, which had similar matching interests and complementary knowledge in addition to contacts and funds available to fulfil a commercialisation plan all the way, hopefully to the market. In addition the Sandlie group argue that the strategy they chose, rather than the alter-

native of establishing their own company, also benefits society because new drugs then have the chance of getting onto the market more quickly.

Inger Sandlie received the first Innovation Prize awarded by the University of Oslo, in 2011.

In the final Chapter 4, Erik Fosse of Oslo University Hospital writes that the new technologies imply a colossal change in the way hospitals are organised and pose several challenges to the health care system. Larger and highly specialised clinics with standardised diagnostics and interventions are developed at the cost of small units that up to recently were governed by the physicians. Quality assurance following industrial standards is adopted. The new, centralised clinics are governed according to cost efficient corporate models. Cultural clashes between the professions occur. The conflicts tend to slow down the development of the new type of health services. While most people want hospital services of industrial standard, they wish at the same time to know who is the doctor taking care of the treatment.

New types of scientists – physicists, computer scientists, engineers and mathematicians – are needed in the specialised clinics, in addition to the physicians and nurses. The continuing development of the advanced methods and medical equipment require research and testing before clinical application. The specialised training of the personnel has to be continuously developed. The Intervention Centre at Oslo University Hospital has been established with the purpose of contributing to well-functioning technological practices in the new industrialised hospital clinics. New types of hybrid clinics combining catheter-based interventions with open surgery are developed, e.g. for heart valve replacement.

The new techniques are better, more efficient, imply cheaper treatment, reach many more patients and result in lesser side-effects than previously had been accepted. The new imaging techniques for diagnostics include magneto resonance (MR), computed tomography (CT) and positron emission tomography (PET). The transition to modern laparoscopic surgery is illustrated, with removal of the gall bladder as an example. Robotics-aided prostate ectomy is nowadays carried out with 10–20 operations per week per new regional clinic, compared to about 20 open-surgery procedures an-

nually per older, local clinic. Percutaneous coronary intervention (PCI), or angioplasty, a recent non-surgical procedure for treating narrow arteries, was performed on 12,000 patients in 2012. The method has, by and large, replaced open heart surgery.

The new minimal invasive techniqies imply shorter stays in hospital. This trend moves follow-up, rehabilitation and nursing to the primary health care services, making communication and co-operation between them and the hospitals essential.

The fifth presentation at the Symposium, entitled "Technical medicine in tomorrow's health care", was not written up as a book chapter.

June 2014, John Grue and Anne-Brit Kolstø

Contents

Health Technology for Better and Safer Services

Bent Høie
Minister of Health and Care Services

Many, including those who work in the health service, have said they do not envy me my post as the Minister of Health and Care Services with the difficult issues and priorities that will inevitably come to my desk. I think the contrary. I am pleased to be working with an area of politics where I and many others have a strong commitment and a lot of opinions. Health concerns us all. The field of health policy is demanding, but also indeed very inspiring.

Part of what makes the biggest impression on me as a health politician, is my meeting with patients and their relatives, and not infrequently health care professionals, who share their experiences as well as the challenges they have met.

Our ambition is to build a health service for the patients – this also means better and safer health care.

On behalf of all patients I will say: No decisions are made about you, without you.

I want the patients, the users and their relatives to participate in improving the services. Quality should be viewed from the patient's point of view. Patients are our most important agents of change, their needs should guide

how we organise the health and care services and technology. Research, innovation and technology must have the patients' needs and perspectives in mind.

The Internet is here to stay, the same goes of course for the "health apps". These technological developments give us as patients and users new opportunities, but it is important that they are used sensibly. At the same time, I would like to stress that new technology is a supplement to clinical care, not a replacement. Technology will never substitute the importance of the presence of health care personnel. Good advice on using these apps is posted on the national health portal "helsenorge.no".

The Sundvolden Platform

The modern challenges in the health and care services must be met with new knowledge and innovation. The Government has stated in the Sundvolden Platform[1] that medical research should be given higher priority, especially regarding serious diseases and the prevention of lifestyle diseases, and that the initiative on welfare technology should be strengthened.

This Government will maintain a strong focus on innovation, research and technological developments. Through the use of new and improved ways of working in the sector, and new ways of delivering service and innovation, we aim to improve both quality and patient safety.

ICT (information and communication technology) is an important tool to achieve better health and a state-of-the-art health and care service – as well as a better life for most people, patients and health care professionals. I do not think our ambition can be achieved without ICT.

The HealthCare21 Strategy

In June this year I will receive the first national multisectoral strategy for research, development and innovation for the health and care services, named the HealthCare21 Strategy (HelseOmsorg21-strategien).

I have very high expectations! It will cover the entire value chain from research to innovation and the development of industry and commerce, the

1. The two parties in the Government have agreed on their politics in a joint paper called the Sundvolden Platform.

development of new patents and products, innovation in the public sector and new ways to organise parts of these services. The Strategy is an important contribution to the development of new policies for health research and innovation in the years to come.

I do understand that the population also has high expectations regarding the health and care services. These expectations initiate debates on the dilemmas and difficulties in setting priorities. I hope that the HealthCare21 Strategy will give us some new ideas on how to work with research and innovation in the coming years and how to organise the health-care services in the future. Many players are involved in creating the Strategy. The participants represent industry, the health and care services, user organisations, academia etc. This symposium gives me the opportunity to thank all of you for the work you do for the Strategy development.

Technology should benefit the patients. New technologies must be safe, should improve the results of treatment and also be cost effective. New technologies should support the services and at the same time increase the efficiency of time and resources spent by health-care personnel.

The public sector should be a driving force for innovation. We need to find better solutions, to apply in new areas the knowledge we already have – as well as develop new products.

The Government will increase access to experimental treatments and promote more clinical trials in Norway. We will ensure funding, a supportive infrastructure, and a decision structure for clinical trials. Patients should get access to new treatments using new technologies or new drugs. Clinical trials and experimental treatment are important means to ensure this.

Technology

New technology and expectations of the technology are the driving force for development.

By means of genomic sequencing, we envisage that in the future we can select which patients will benefit from one type of treatment or medicine and who will not. The progress in personalised medicine must be met with knowledge. I will be handed a report on this issue from the regional health authorities during 2014. We will then be better prepared and can facilitate a future oriented use of personalised medicine in the health services

that also takes into account important issues on ethics and patient participation.

Many point to the possibilities that new technology can provide for more effective treatment. Some are concerned that «tailored medicine» will result in more expensive treatment. It is important for me that the medication given is the best suited for the individual patient. It is also possible that this development will become more cost-effective in the future.

ICT

Norway has a Government that puts modernisation and innovation high on the political agenda. Modernisation is a priority for this Government. Because of this, ICT is one of eight high-priority issues for the Ministry of Health and Care Services. I have also appointed a Secretary of State with responsibility for this area, Cecilie Brein-Karlsen.

We have high ambitions for digitalisation in the public sector and in society as a whole. The Minister of Local Government and Modernisation, Jan Tore Sanner, has the primary responsibility for this. Smart, efficient and comprehensive use of ICT is perhaps the most important means we have to achieve better health with increased efficiency and more patient empowerment. The Government will establish a scheme to finance investments in ICT. This is also important for the development of research infrastructure.

We will strengthen national co-operation on ICT in the area of procurement. With many independent entities, it is necessary to clarify national responsibility for the IT development, and to establish a clear division of roles and tasks among these entities. A special health authority has been created for strategic co-operation on ICT in the hospitals. The main office will be in Bergen.

The vision of the White Paper "One Patient – One Record"[2] remains unchanged. We will be closely focused on the follow-up of this White Paper and aim to implement the following visions:

2. The White Paper is a report to the Norwegian Parliament; Meld. St. 9 (2012-2013) Én innbygger – én journal" http://www.regjeringen.no/nb/dep/hod/dok/regpubl/stmeld/2012-2013/meld-st-9-20122013.html?id=708609 [in Norwegian]

- Health professionals should have user-friendly and secure access to patient information.
- Citizens should have access to user-friendly and secure digital services.
- Data should be available for quality improvement, health monitoring, management and research.

Health professionals need to have secure access to necessary patient information: referrals, discharge notes, medication, test results, X-rays etc.

This spring, we aim to promote a bill that ensures that appropriate patient information follows the patient throughout their treatment. The patient, not the institution, is thus placed at the centre.

Good patient treatment includes protection of personal privacy. Technology can, in my view, ensure privacy better than a key to a doctor's office or hospital files. Appropriate technology provides control concerning who has, shall have and has had access to patient health information. I think the protection of privacy debate must be moved from that of a paper-based society to a discussion on how privacy best can be achieved in a modern society where health information is digitised.

We must build an ICT infrastructure comparable to an effective highway that is not stopped by low speed limits, tolls and ferries.

In several places in the country the health-care services have established solutions to give patients easy and secure access to their own digital health information. A project called "Western Patient" run by the Førde Hospital Trust gives the patients a digital overview of their appointments at the hospital. A notification by SMS is sent to patients who have an appointment at the hospital.

Digitalisation gives us real influence over our own treatment – and new ways to empower patients and citizens to take charge of their own health care**.**

Secure access to data gives better quality. Up-to-date data needs to be available electronically. This requires that reporting to registers should occur as an automatic process. Comparison of such data will enable development in the health status of the population to be reliably monitored and allow the needs for health and care services to be systematically evaluated.

I think that digitalisation is necessary to create patient-centred treatment. At the University Hospital of Northern Norway, an Internet solution is available that provides patients with chronic kidney failure an option to choose among different treatment alternatives. Patients can choose the solution that they find most suitable, based on their own needs. And this is not necessarily the most expensive solution.

Medical equipment makes life easier and safer when patients are diagnosed, treated and monitored, and also enables disease prevention. These are priorities that are important for this Government.

The Ministry of Health and Care Services established a new system for the evaluation of new methods in 2013. This system shall prevent new medical technical equipment being arbitrarily taken into service without a prior health technology assessment. The aim is to improve quality, increase patient safety and support a more equitable prioritisation of resources.

Another area where we will apply ICT is for increasing the focus on welfare technology.

Welfare technology gives humans the ability to cope with their lives and health and to stay longer in their own homes despite suffering from illness, problems or disabilities. Welfare technologies can put the users' needs at the centre and provide better utilisation of resources. For example, security packages with GPS and various sensors may improve safety in everyday life. The welfare technology must meet the requirements of both the users and the service providers before implementation. Personnel should not be replaced by technology. At the same time, many people embrace the independence welfare technology can provide. Going forward, we need both personnel and a wise use of welfare technology.

The fact that municipalities do not always adopt the ideas and solutions is not necessarily an expression of reluctance or inability to innovate. It is just as much an expression that the ideas and solutions may not fit the needs and gaps in their particular service. New technological solutions and ideas change work methods, organisation and skills required, so that sometimes the transition itself is perceived as too demanding.

Several of the working groups that have been established in the HelseCare21 initiative have pointed to the need for a strong focus on research, innovation and education in the municipal health and care services. We will

stimulate local innovation and development. Innovation will also promote Norwegian industry in this area.

The Ministry has followed up the recommendations in the White Paper on "Future care"[3] and established a national programme for the development and implementation of welfare technology. The main objective of the programme is to make welfare technology an integral part of the care services by 2020. In 2014 we have therefore allocated 34 million NOK to a welfare technology programme.

As I have said, and often repeated, patients and the users shall be deeply involved in the development of new ideas and new solutions. I want them involved from the start; diagnosis through to definition of the solution, including options of new solutions as they become available, and through the period of treatment and after-care.

I want you all to use the energy you have to evolve new ideas and knowledge. I believe in competition in this field. Several centres should be leading in innovation and new developments, each of them in a field where they excel. If we as politicians point out only one winner, I think we will ruin your positive energy.

It is important to have high demands. At the same time it is important to improve conditions so that the technology can contribute effectively to achieve our ambitions for easy and secure access to digital services for citizens and health professionals. The data must simultaneously be available for quality improvement, health monitoring, research and innovation.

To create transparency and predictability in the sector, this Government will promote a National Health and Hospitals Plan. This will clarify the national responsibility for ICT development and ensure clear role and task sharing across the health sector. The Plan will lay the foundation for a new, smarter and better management of the hospitals. We have already started this work. I look forward to a broad approach with strong involvement from you all.

3. The White Paper is a report to the Norwegian Parliament; Meld. St. 29 (2012-2013) Morgendagens omsorg http://www.regjeringen.no/nb/dep/hod/dok/regpubl/stmeld/2012-2013/meld-st-29-20122013-3.html?id=735302 [Summary in English] http://www.regjeringen.no/nb/dep/hod/dok/regpubl/stmeld/2012-2013/meld-st-29-20122013.html?id=723252 [Full edition in Norwegian]

We will carry out changes that give such good results for the patients to come, that they become unthinkable to reverse. We will create the patients' health service, and use technology in a way that involves the patients in a different way than it does today.

Innovation for Health in Developing Countries

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Introduction

We witness disturbingly high rates of infant and child mortality in developing countries. While Norway experiences 3 deaths per 1000 live births, Sierra Leone has 119[1], forty times the Norwegian rate. And this is just one sign of massive public health challenges. Developing countries struggle with persistent communicable diseases (malaria and HIV/AIDS the greatest killers) and an emerging double burden as non-communicable diseases (e.g. obesity, diabetes) are striking also these countries. National health-care systems are doing their best to meet the situation, but almost everywhere are struggling with limited resources, too few skilled health-care workers and large differences in health service availability between urban centres and rural and remote areas.

1. United Nations Inter-agency Group for Child Mortality Estimation (UNICEF, World Health Organization, United Nations Population Division and the World Bank), 2011.

It is widely acknowledged (by e.g. the World Health Organization (Savigny and Adams, 2009)) that improved reporting, communication and co-ordination of health initiatives are cornerstones to help alleviate the dire situation in developing countries. Aptly called "stumbling in the dark" (The Lancet, 2005), the lack of reliable data on for example births, immunisation coverage and child mortality rates, is a key concern raised by the World Health Organisation. Without reliable data, evidence about the prevalence of child mortality and lack of access to health services remains anecdotal. The paucity of information becomes both a symptom and a cause of underdevelopment (Okonjo-Iweala and Osafo-Kwaakoa, 2007). It is an obstacle to tracking health needs, judging the magnitude of problems, designing health programmes and assessing their effectiveness. This challenge is ubiquitous, confined neither to health programmes, nations, or international health agencies and organisations.

Health data and information systems are not absent in developing countries. Typically, international donors set up their own and collect data as parts of their health initiatives and programmes. This results in a situation where health centres, hospitals and districts find themselves using a variety of different information systems – one for each initiative. Furthermore, the data that is collected typically becomes fragmented, duplicated and of poor quality. A regional assessment[2] of the health information systems in West Africa by the University of Oslo, commissioned by ECOWAS (Economic Community of West African States), confirmed that integration of health information systems is a key challenge. The main factors that contributed to this situation, beyond unco-ordinated donor activities, were the absence of standards and guiding policy frameworks.

In this context of overwhelming health challenges and information systems patchworks, there has been an explosion in mobile phone ownership. In just a few years, mobiles have become accessible in areas where no other infrastructures like electricity, clean water and banks exist (e.g. The World Bank, 2012). There are now more than 4.5 billion mobile phones in developing countries, as against 350 million PC's (International Telecommunication Union (ITU)), a ratio of almost 13:1. And only 11 million hospital

2. "Situation Assessment of Health Information Systems in the ECOWAS Region", Final Report, Commissioned by the West African Health Organization (WAHO).

beds (The World Bank, 2002). While the poorest-of-the-poor may not afford mobiles, health-care workers typically can, and generally already have them. Mobiles thus represent an opportunity to engage with and improve the grim situation by strengthening health systems in terms of reporting, communication and co-ordination. Using **mobiles in health care (mHealth)** is an emerging research area with, for example, the discussion by Khan et al. (2010) on the needs and opportunities for mobiles in developing countries, a special issue in the Journal of Health Communications in 2012 (issue 4), and the establishment of the dedicated Journal of Mobile Technology in Medicine in 2012. This literature has already identified a pressing need to progress mHealth from promises, potentials and pilots. It questions whether mobiles are anything more than just a hype (Nielsen and Fjuk, 2010). While the potential in mobiles is obvious, there is a need to demonstrate that mHealth really can make a difference over time and beyond pilots, at a national or regional scale. And that it will justify both local and regional investment of money and human resources.

The **Health Information Systems Programme – HISP**[3] is a global network established to strengthen health information systems in developing countries, managed and co-ordinated by the Department of Informatics at the University of Oslo. HISP was initiated based on activities in post-apartheid South Africa in 1994. Since then, HISP interventions have been based on action-research and supporting learning across developing countries and regions in close collaboration with ministries of health. As an action-research project, HISP has developed the **District Health Information Software DHIS 2**[4], offering a systematic and integrated approach to strengthen health information systems with respect to the collection, validation, analysis and presentation of aggregate statistical data used for health information management activities. DHIS 2 supports different devices such as mobile phones, tablets and PCs. It also offers the back-office system to aggregate and analyse data. DHIS 2 is currently in use in more than 46 developing countries across four continents. DHIS 2 is free, open-source software, released under the liberal Berkley Software Distribution[5] licence.

3. For more information, please see www.hisp.uio.no
4. For more information or to download the software, please see www.dhis2.org
5. See www.linfo.org/bsdlicense.html

Technical and implementation support and training activities are offered by HISP and local partners on a not-for-profit basis and typically sponsored by donors such as Norad (The Norwegian Agency for Development Cooperation), PEPFAR (The U.S. President's Emergency Plan for AIDS Relief) and the Global Fund (an international financing institution that fights AIDS, tuberculosis and malaria).

In the following sections we discuss the way HISP utilises DHIS 2 and mobiles in the context of developing countries, and how we work to meet the challenges in developing countries introduced above. The discussion will be framed in relation to innovation in both technology and capacity building. We see innovation in this domain as new and different ways of doing things to strengthen health-care systems – as changes in thinking, products, processes and institutions.

The DHIS 2 Software: Innovation in Technology

Since health information system requirements in many developing countries are similar, it makes more sense to collaborate than to work in isolation. DHIS 2 is therefore based on a distributed development approach. The software is developed in a network of development, implementation and use activities, involving regional and country health authorities, open source communities and research institutions. To support this distributed development, DHIS 2 is open-source based. This means that the code base is openly available to anyone to work with and extend[6]. And instead of being based on a business model where the users are paying for licences, the cost of software development is distributed among those involved in its development. Norad and the University of Oslo have been instrumental in financially supporting the core DHIS 2 software development activities.

DHIS 2 offers support for health sector reforms that aim towards decentralisation and the development of health districts by integrating the vertical flows of data from various health programmes at district level. DHIS 2 is used in many countries as a central data warehouse. And in West Africa, it has been selected to provide a regional data warehouse for 15 countries, with a shared list of indicators for reporting. The strategy of HISP is to

6. Available at: www.dhis2.org

build on what already exists – the installed base of existing information systems. Thus, DHIS 2 is designed to manage a wide range of integration scenarios with services from other applications and perform transformations of data through flexible routes, from for example Electronic Medical Records (EMR), Human Resources (HR) and Logistics Management Information Systems (LMIS).

DHIS 2 offers a suite of different technologies. This extends the reach down to the lowest level of the health-care system. It enables health-care workers and managers to use the device they have access to at the moment (typically at point-of-care) – from high-tech to low-tech. They can submit data via SMS, Java applications, through a mobile phone browser, with an Android App or a PC/laptop/tablet (getting data in). And they can access a dashboard (see Figure 1) with their data, reports and graphs to support their decisions (getting data out).

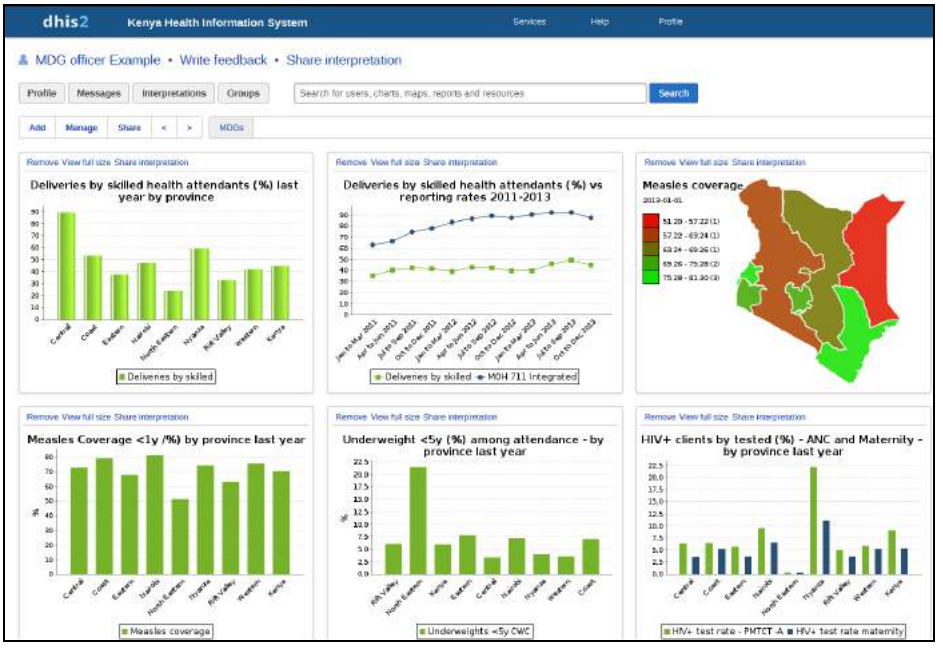

Figure 1. Example of DHIS 2 PC dashboard from Kenya.

The dashboard on the different devices is configurable centrally as well as for end-users. User-made dashboards composed of a set of different views,

indicators and graphs can also be shared among users. The information can also easily be made available on an open web-portal to make key health indicators publicly available. Mobiles offer an opportunity to connect and exploit new developments such as the new fibre cables down the coast of West Africa. Acknowledging this potential, DHIS 2 supports wireless connectivity from mobile devices and PCs with mobile Internet modems (see Figure 2).

DHIS 2 is designed to operate in the low-resource setting of developing countries, using available technology (e.g. basic mobile phones) and innovating with the latest technology (e.g. mobile Internet, HTML 5 and cloud services). HISP leverages on the fact that **in developing countries, Internet is mobile Internet** and the commonly available devices are mobiles. HISP continuously connects and adjusts to what already exists on the ground in terms of health information systems, infrastructure, devices, hosting environments and human capacities. And while exploiting the newest of technologies, HISP continues to support old, well proven and broadly available technologies. These configurations are outcomes of close and long-term interactions between HISP and users in a range of pilot and implementation projects.

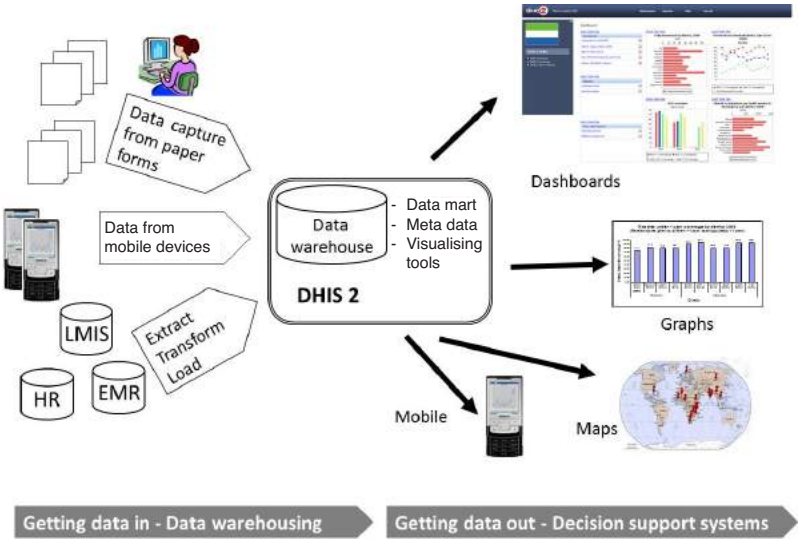

Figure 2. DHIS 2 Overview.

DHIS 2 as the First National Online Health Information System in Africa

In 2010, the Kenyan Ministry of Health opted for DHIS 2 and planned to implement an online system. The Internet coverage across the country was uncertain and serious doubts lingered about whether all districts (approx. 200 at that time) would be able to connect. Experiences with DHIS 2 in Sierra Leone in 2007–2009 had shown that stand-alone installations require a large maintenance team to keep all the local installations functional, virus-free and up-to-date. And with a stand-alone approach, the different levels of the health system each have to compile their data before manually passing it on to the next level, and so on. This was something to avoid.

During pilot testing, frequent power outages showed that fixed-line Internet was too unstable. At the same time, mobile phone networks were up and running. Mobile Internet modems were tested with success around the country and by the time the roll-out was completed in October 2011, it was clear that all the districts and district hospitals in the country could use the online DHIS 2.

But while many new facilities in the health system were online, they suffered from fluctuating mobile connectivity. To deal with this, offline data entry was enabled by making use of the local storage in the browser (enabled by the HTML 5 standard). The form and its data are stored on the end-user device (mobile phone, tablet or PC) allowing data entry to continue seamlessly when connectivity is broken. Data is automatically submitted to the server when the device is back online. Further, to enable offline data analysis a small desktop application (data mart) was developed, allowing users to download their own data from the server and then connect Excel PivotTables to this local database. This approach only requires local offices to have an Internet browser and a mobile Internet connection. Another key feature with this online approach was that it supported rapid piloting at a national scale in Kenya. When addressing numerous user requests, changes were implemented for all online users immediately, enabling a new and more direct way to conduct user-driven design and innovation.

This country-wide health information system with a national online server was unique at the time and revolutionised the health management data completeness and timeliness of data reporting in Kenya. Going from a dysfunctional system with major problems of reporting from the districts,

Kenya reached about 80 percent data completeness shortly after completing the roll-out. Since January 2012, just three months later, the completeness has stabilised just above 90 percent for all the major forms, a major achievement and an important foundation for a well-functioning health information system.

The project in Kenya showed that with mobile Internet connectivity, DHIS 2 can also be implemented through a centralised online server, rather than via multiple regional installations. This experience and knowledge is now used in other DHIS 2 implementation projects. This renders superfluous a large number of installations, like one for each district office, hospital or other user site, radically reducing maintenance costs. It eases implementation on a national scale, and the issues of local hardware, software versioning and maintenance are replaced by a much simpler online maintenance scheme. At the same time, however, such a centralised approach puts a lot of trust and risk on the central server, as all users depend on the server to be up and running at all times. To deal with cases where the local Ministry of Health is not able to host a central server (due to e.g. poor connectivity, lack of proper power back-up, insecure server environment or lack of hosting competency), HISP supports hosting the server elsewhere, at least as a provisional solution. In such a cloud-based environment, HISP has in some cases taken the role of configuring and maintaining the server to speed up implementation processes and offer support until local capacity is in place.

The HISP Network of Action: Innovation in Capacity Building

A well-functioning information system is a prerequisite for a strong health-care system. But a tablet with a mobile Internet modem for each health-care worker and a central database with accurate and timely data will not alone improve the health situation. The information must also be relevant across the health-care system and be used for health management decisions. This is reflected in the DHIS 2 software development strategy, focusing both on reaching managers with relevant data, and reaching out to the lower-level facilities and communities.

Health information systems in developing countries tend to degrade over time (Braa et al., 2004). An essential lesson learned from 20 years of

HISP activities is that sustainability can only be achieved by strengthening local human capacity. Local resources have to take a key role in the implementation of the system, and they need to be linked to a larger supporting network locally, regionally and globally. To be sustainable, health information systems require operative activities, system maintenance, educated users and institutionalised information use. To support local capacity building and information use, HISP arranges DHIS 2 Academies and conducts action-research (described below).

DHIS 2 Academies

HISP established the DHIS 2 Academy programme in 2011. The Academy is a series of regional training seminars in West Africa, East Africa, Southern Africa, Asia and Latin-America. It is dedicated to DHIS 2 implementers and trainers at regional and country level. The Academy is an intensive training programme with both theoretical/conceptual and practical sessions. The participants learn the principles of the DHIS 2 design and how to set up and maintain DHIS 2 to support their organisation's data collection, analysis and reporting needs. This is addressed from a technical perspective, providing a better understanding of the available DHIS 2 software tools and their best practices, as well as from the health management side through sessions on data quality and information use. This acknowledges that health professionals skilled in analysing indicators and data quality constitute a necessary ingredient in a health information system. At the Academies, DHIS 2 experts are also available to guide participants on practical work with their DHIS 2 implementations, whether it is in an initial or more advanced phase, e.g. help designing data sets and collection tools, or indicators and reporting outputs (charts, dashboards, maps, pivot tables etc.). Some of the experts are from the University of Oslo, while others are local experts with long-term experience with DHIS 2 and other health information systems.

Starting out with a model where participation was sponsored through HISP as few were willing to pay for their own participation, most countries today find it worthwhile covering the costs of sending participants. To address a rapid growth of requests for more Academies and training workshops, the DHIS 2 Academy programme is currently being scaled up to

include an online component as well as more tailored and specialised training sessions catering for several types of participants and DHIS 2 topics/interest areas.

The training strategy is based on Training of Trainers; developing local capacity that can adequately cover training needs for the majority of DHIS 2 users. The responsibility of hosting, arranging and teaching is gradually being transferred from the University of Oslo to local expertise. This approach builds on developing local or regional institutional bases for capacity building with a basis in a local university and related master's programmes, or in a strong NGO. The longer-term aim of the DHIS 2 Academy is to build a community of DHIS 2 users and experts in different regions. This community must be rooted within a network of regional and local partner institutions for long-term sustainability. Thus, HISP will continuously seek to support the strengthening of existing institutions and NGOs, and establish new ones.

Capacity Building Through Action-Research

Academic institutions and education are at the top of the HISP capacity-building pyramid, and HISP has so far graduated 24 PhD students at the University of Oslo. Through research and education grants, HISP has supported the establishment of academic capacity in health information systems at universities in Ethiopia, Malawi, Mozambique, Sri Lanka and Tanzania. And nine master's programmes have been established in partner countries, funded by the Quota scheme[7], the Norwegian Centre for International Co-operation in Education and the Norwegian Research Council. The DHIS 2 software development and its implementation projects were initially action-research based, and many of them still are. Action-research based in the sense that new functionality and software features are tested out on a small-scale on the ground as research projects before being scaled up, and if then successful, taken back and implemented in the DHIS 2 software core (e.g. offline support, central hosting, mobile Internet modems). In parallel with software successes, important implementation experiences

7. Funding scheme offered by the Norwegian Government to students from developing countries in the South and countries in the Western Balkans, Eastern Europe and in Central Asia.

are documented in the academic literature and shared at events such as Academies.

While HISP rapidly embraces relevant technology innovations and the possibilities they offer, innovations are only implemented in the core when a deep understanding of business processes and user needs has been established. Core innovations are subsequently made available in a DHIS 2 software release and propagated to the larger user community, announced and discussed on social media as well as at DHIS 2 Academies. They can then be implemented locally where found relevant. In parallel, innovative approaches and best practices are shared and discussed in the broader information and communication technology (ICT) for the development research community. Equally important, action-research also relates to building knowledge about how to implement health information systems in a sustainable fashion. This includes for example approaches to building alliances and networks of partners, building local resources with the expertise to educate users and to implement, host and maintain DHIS 2 over time. The experiences from implementing DHIS 2 are accumulated and used in later projects. While these lessons come from health information systems software and implementations, they are also made relevant more widely to implementation of ICTs in developing countries.

Through participating actively in a range of implementation projects, HISP has managed to develop highly relevant software and establish an implementation approach that has shown itself sustainable. As a part of this, HISP generates high quality research outputs through PhD students, many of whom return to their home country to lecture at universities, support local companies and support and give advice to ministries of health, donors and NGOs. Thus, they become key players in the establishment of local and regional nodes to support the strengthening of local expertise and health information systems.

Rapid Implementation in Uganda Based on a Network of Experts

Uganda became the third country in Africa to implement a nationwide online DHIS 2 system, in August 2012. The first preparations of the Ugandan implementation started in August 2010 when the CDC (Centers for Disease Control) initiated contact with HISP. CDC and other partners working with

health information systems in Uganda gradually got the Ministry of Health and other key stakeholders to consider DHIS 2 as the new national health information system. Four Ugandans (from MoH, CDC, and a PEPFAR/USAID project) attended the first DHIS 2 East Africa Academy in Dar es Salaam in 2011. Here, they met with the Kenyan team who at the time where in the midst of the above-mentioned national roll-out process. This training was a major step forward for the Ugandan implementation; important lessons from other countries were learned from experts and peers and a team of four very competent people was established.

A few months after the Academy, the Ministry took the decision to roll out DHIS 2, starting with a pilot in four districts in Western Uganda early 2012. In January 2012 a trainer from HISP Oslo conducted a Training of Trainers course in DHIS 2 and supported the first training sessions in the four pilot districts. The districts were the Saving Mothers Giving Life (SMGL) pilot districts, and the idea was that these could quickly start to use DHIS 2 to capture data on maternal health. The initial support from Oslo was paid for by the University of Oslo (through Norad funds), as the Ministry did not have the funding arrangements in place. A few months later a PEPFAR/USAID project came up with funding for a second round of training, with trainers from Oslo and Kenya. In June, the Ugandan technical support team with members from MoH, CDC and PEPFAR/USAID started the national roll-out, and in September, only 4 months later, all districts where using DHIS 2 online and reported monthly data. This rapid roll-out was organised as a collaborative effort involving many different partners, where each partner was given one or more training seminars to support financially. Based within the HISP network of action, the Ugandan team could draw upon experiences and expertise from the University of Oslo as well as Kenya.

Innovative Approaches in Search of the "Missing" Data

Saving Mothers Giving Life (SMGL) is a global initiative launched in 2012 to strengthen maternal and new-born health, with the Governments of Norway and USA as the key contributors. Four districts in Western Uganda were among the pilot sites, and data collected through DHIS 2 has been instrumental in supporting monitoring and evaluation of the local life-saving

initiatives. While big and expensive demographic and health surveys have documented alarming rates of maternal deaths in many African countries, including Uganda, there are major gaps in the routine data on maternal and neonatal deaths being collected in the health system. With as much as 50% of the deliveries taking place in the communities and outside the health facilities, these critical community events are not being recorded on a routine basis, which makes it very difficult to monitor the progress of interventions. To address this missing data problem, Village Health Teams (VHTs) operating in the local communities in Uganda were trained to report maternal and neonatal deaths using short messaging services (SMS) from their mobiles directly to the national online DHIS 2 system. In addition to feedback on their reported data, the VHTs also received educational messages and other key information on SMS from DHIS 2. Establishing this critical communication link, between the national health information system and the community health workers operating in the remotest areas, was highlighted in the SMGL Annual Report 2013[8] and referred to as "fundamental to the initiative's ability to measure and evaluate the impact of its interventions". Monitoring initiatives to strengthen maternal health requires integrated analysis of data from many different sources including service data, commodity availability, human resources and community data, as well as more detailed data from facility registers and death audits. The Ugandan DHIS 2 team has been innovative in utilising the flexible architecture of DHIS 2 as well as a range of mobile clients to capture this data. In doing so, they have pushed the DHIS 2 core development forward with new requirements and innovative approaches. These activities related to maternal and child health data in Uganda include:

- Monthly summary data – on paper from facilities, onto DHIS 2 from the districts using mobile Internet modems.
- Weekly Option B+ (prevention of mother-to-child transmission of HIV – PMTCT) data, 10 key items reported on SMS directly from the health facilities, including access to commodities (HIV test kits and antiretroviral therapy).

8. http://www.savingmothersgivinglife.org/our_work/annual_report.aspx

- Weekly village health team reports on neonatal and maternal deaths in the community (SMS).
- Detailed maternal and neonatal death audits on individual cases.
- Tracking of mothers and children using reminders and data capture of each visit to the clinic (SMS).
- Interoperability with the human resource information system (iHRIS) to bring in more accurate staffing data for each health facility.

When combined in one integrated data repository, this data provides a unique basis for monitoring interventions on maternal and new-born health.

Many of these innovations were developed in the field in Uganda through collaboration between the HISP team and the local Ugandan DHIS 2 team. The testing and feedback from the Ugandans have been instrumental in making these features part of the core DHIS 2 releases available to all countries.

Contributing to Development through Research-Based Innovation: From Pilot to National Systems

Health challenges are global challenges – they are our challenges. The motivation behind HISP lies in three core challenges in developing countries. First, there are substantial differences in the access to infrastructures and human resources and in particular between urban and rural areas. This social inequality is reflected in the health of the most vulnerable: mothers and children. The challenge we embark on is to provide health-care workers with technologies, solutions and information that supports them where they work – bridging this digital divide. Second, health information systems in developing countries are struggling with fragmentation as a result of multiple parallel systems. Health managers are in need of information across these systems to make the right decisions; integration is central. They need support in their "search of the missing data" (Kanjo, 2012). Third, there is a critical lack of competence related to health information and health information systems, and thus a need to strengthen expertise at universities and in their programmes, and also within NGOs and private companies.

HISP as a network of experts has been developed through mutual synergies between software development, implementations, training, education

and research. Its footprint and reach is currently increasing as new countries and organisations are implementing the software. At the same time, new global donors, NGOs and small companies in developing countries (offering training and technical support) are entering and strengthening the network. Through use in multiple contexts, DHIS 2 is gradually becoming a global standard, and is described by a Lancet article as "the biggest implementation of open-source health information systems [in the world]" (Webster, 2011). This is an excellent example of how innovation at the University of Oslo has made an impact outside academia, as recognised by the University of Oslo in rewarding its Innovation Prize to DHIS 2 and HISP in 2013. This successful growth is an outcome of innovation on multiple levels:

- Technology (mobile Internet, cloud computing, integration, etc.).
- Processes (networks of experts, sustainability based on capacity building, etc.).
- Business models (non-profit, open source, network of partners, etc.).

HISP is continuing to fight the battle to reduce the gap left by independent programmes collecting loads of data relevant for themselves, but nothing for other vast and important areas. Health information systems' architectures are seen as a way to try to organise the increasing number of systems into a 'system of systems'. One possible way forward is authoritative electronic registries that provide shared standards for data and indicators, identification of health facilities and licencing of health providers.

HISP must navigate tactically, and continuously adapt and develop DHIS 2 to keep it relevant for its users. At the same time, the long-term HISP strategy and focus is on a sustainable software core and sustainable implementations and improvements in the health-care systems where it is implemented, by nurturing our network of experts. By doing so, our aim is to offer one crucial piece in the puzzle to improve the health situation in developing countries.

It is not straightforward to formulate a cookbook for the successful development and implementation of sustainable health information systems in developing countries, though there are some general principles, and these we believe are relevant also outside the remit of HISP:

- Start small and solve real problems.
- Implement a scalable approach from day one.
- Use mHealth to extend and strengthen the existing national health systems.
- Build local capacities and nurture local, regional and global networks of action.
- Use the Ministry of Health as a co-ordination body.
- Pursue partnerships to gain momentum for integration.
- Support the widest range of available technologies.
- Embed social features into information systems to support peer capacity building.
- Work towards a shared, open information repository.

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From Basic Research to Innovation

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Introduction

Would you rather take medicine several times a day or every third week? The possibility emerged as a result of research that was aiming to solve other problems.

Join us on a journey that begins with Professor Francis Brambell (1901–1970) in North Wales who studied rabbit reproduction. In the early 1930s he discovered that antibodies can be transmitted from the mother to the rabbit foetus. Brambell's research now takes on a rebirth, and will be important for tomorrow's medicine. Today we understand the mechanisms behind Brambell's discovery. We understand the molecules involved. This now opens new doors for application. In this article we will show the way forward to new innovative knowledge about medicine.

We will show how molecular basic research can take a completely unexpected direction, in this example from antibody studies to new strategies for drug development.

And how keen observations during clinical practice at Sørlandet Hospital led to an innovation that can become a new drug to help thousands of patients with neuropathic pain.

In the first case, strategic choices led to collaborative work with Novozymes A/S, a large biotech company which is a major manufacturer of albumin.

In the second case, there was the choice of setting up a start-up company to develop the drug or to licence the rights to develop the drug to the Big Pharma company most dedicated in the field.

Antibodies and the neonatal Fc receptor (FcRn)

Antibodies provide protection against infections. Since we are surrounded by bacteria and viruses that can cause disease, we would not have managed without. Antibodies of the IgG type are found in blood, as is albumin. Both molecules circulate for a long time in the bloodstream. While all other proteins are broken down within hours or a few days after they are produced, the half-life of albumin and IgG is three weeks.

Whilst looking into this, we became aware of Francis Brambell's work. Brambell was head of the Zoology Department at Bangor University in Wales. During his investigations of rabbit reproduction, he discovered that the mother rabbit's IgG was transferred to the rabbit foetuses (1). There was no question of a leak, but rather, an active and selective transmission. To examine the transport mechanism, Brambell took IgG from the blood of the rabbit mother and split it into two parts, Fab and Fc, with an enzyme. Fab is the part that normally attaches to bacteria and viruses, and Fc is the part that normally binds to molecules that ensure that the viruses and bacteria are killed. While Fab varies from one antibody to another, the Fc portion is the same for all antibodies of the same type.

Brambell injected Fab and Fc fragments into pregnant rabbits in separate experiments and found that Fc fragments, like IgG, were transported to the foetus, but Fab fragments were not. He also discovered the long half-life of IgG in blood, and argued that it might be the consequence of protection from degradation, and an active process, just like the transport from mother to foetus (2). He suggested that the active process in both cases relied on the presence of a receptor for Fc.

The following is taken from Brambell's article in the Lancet (1966) (1): "We suggest that attachment to the receptor protects IgG from enzymatic degradation inside the cell and that the receptor is located in the walls of the pinocytotic vesicles. Pinocytosis is well recognized and specific receptors are quite in the most modern fashion; thus the only possible element of novelty is in locating the receptors in the walls of the vesicles and suggesting that they protect the attached protein from enzymatic degradation."

Further research has confirmed Brambell's hypothesis. Thirty years later, the receptor was actually found and named the "neonatal Fc receptor" (FcRn) (3). It is indeed located in small vesicles inside cells that line blood vessels (4). Here, it binds IgG molecules that are taken in by "cell drinking" (pinocytosis). The binding occurs at acidic pH, and FcRn then directs IgG back to the cell surface that faces blood and where the pH is neutral. IgG does not bind FcRn at neutral pH and is therefore released into blood and thus protected from degradation inside the cell. All those pinocytosed molecules that do not bind the receptor, are degraded.

The neonatal Fc receptor binds albumin

We were surprised to find that FcRn binds albumin, as well as IgG (5), but also intrigued, as this explains why both IgG and albumin have long half-lives in blood, much longer than other molecules of similar shape and size.

Jan Terje Andersen, who was then a PhD student at the Department of Molecular Biosciences, University of Oslo, wanted to study this further and soon found that IgG and albumin bind the receptor simultaneously. His research indicated that the two bind to opposite sides of the receptor. He found that binding of one did not affect binding of the other (6).

Figure 1 (next page) shows the shape of human FcRn. The binding site for IgG is shown with yellow spheres while the binding site of albumin is shown with red spheres. Recently, the three-dimensional structure of FcRn bound concurrently to IgG and albumin was reported (7).

Albumin and IgG have completely different roles in the body. While IgG protects against infection, albumin transports nutrients and waste products around in the blood. It also binds many small molecules, such as the therapeutics diazepam (Valium) and warfarin (Coumadin). All bind at distinct pockets on the albumin surface (8).

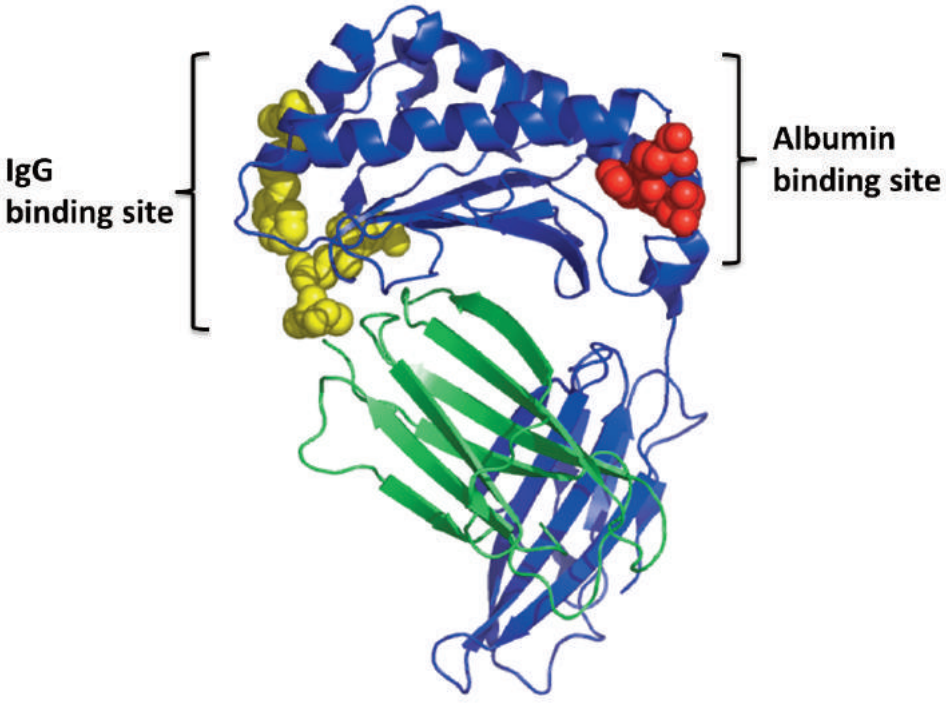

Figure 1: Made using PyMOL software and the PDB accession code 3M17. Reference: Mezo, A.R., Sridhar, V., Badger, J., Sakorafas, P., Nienaber, V.: X-ray crystal structures of monomeric and dimeric peptide inhibitors in complex with the human neonatal Fc receptor, FcRn. J. Biol. Chem. 285(36) (2010, Sept. 3) 27694-701. doi: 10.1074/jbc.M110.120667. Epub 2010, June 30.

After the results obtained by Jan Terje Andersen were presented at a scientific conference, the research group at the University of Oslo was contacted by Novozymes A/S, and research collaboration was established. The collaboration was inspired by numerous studies of the interface between IgG and FcRn, which had led to the design of IgG variants with half-lives that far exceed that of normal IgG. This created great excitement in the pharmaceutical industry and in particular amongst those developing IgG variants for the treatment of cancer and inflammatory and autoimmune diseases. The new IgG variants showed increased affinity and strong binding to FcRn at acidic pH and unchanged affinity and low binding at physiological pH. Could we describe the FcRn contact inter-

face with albumin in detail and also design new albumin variants with a super-long half-life in blood?

Novozymes A/S had already established patented technology where drug molecules were attached to albumin to give them long half-lives in blood (9). Albumin variants with super-long half-lives would give the drugs an even longer half-life, which would be a great improvement.

A major research drive led to important parts of the interface being described (10). This collaborative effort involved researchers from Novozymes A/S, Jan Terje Andersen, and other PhD students in Professor Inger Sandlie's group at the University of Oslo, as well as structural chemists Bjørn Dalhus and Magnar Bjørås at the Department of Microbiology, Oslo University Hospital. The interface was found to include three key amino acids called histidines, which explains why the bond between albumin and the receptor is strictly pH dependent. Histidines are positively charged at acidic pH, and the bond requires the presence of the positive charges.

Then, Jan Terje Andersen became particularly interested in the last stretch of amino acids in the chain that forms albumin. He did a pilot study in which he tested the significance of a small number of amino acids in this area, and found, to his surprise, that the amino acid at position 573 plays a key role. When he then compared the amino acid chains from a whole range of different species, he saw that all have the amino acid proline at position 573, whereas humans and orangutans have lysine. Novozymes A/S made 20 different albumin variants, each with a different amino acid at position 573, and Andersen found that 19 bound to the receptor with an affinity higher than that of normal albumin. Some bound much better, and the variant with proline was among them. In addition to position 573, additional positions were found where mutation enhances binding. They gave an additive effect that increased the binding strength further. Importantly, the albumin variants tested show extended half-lives in pre-clinical models, such as mice and rhesus monkeys (11).

Novozymes A/S is marketing the various albumin variants as the Veltis® technology http://www.veltis.novozymes.com/. The work was published in scientific journals and Novozymes A/S filed a series of patent applications.

Figure 2. Jan Terje Andersen in the laboratory.

Dosage and preclinical testing

Small protein-based medicine candidates, called biopharmaceuticals, may have great clinical potential, but short duration in the body due to rapid degradation or excretion in urine. By fusing them to albumin their half-life increases significantly, which will increase their therapeutic effect (9,12). Not only will the level of the drugs in the body remain constant and high enough to be efficient, the drugs may not need to be administered at high doses that may be toxic for some patients. Last, but not least, the drug may be given less frequently.

The results that we have obtained are therefore very promising and we have great expectations for the coupling of drugs to the new albumin variants. In fact, these albumin variants may revolutionise the use of many drugs for the benefit of patients and the health-care system. We are delighted that our new albumin variants can be of great benefit to society. Some biopharmaceuticals may well be administered as infrequently as monthly or on a multi-monthly basis.

Industry co-operation.

Novozymes A/S is a large biotechnology company with its headquarters in Copenhagen, and the production facilities for albumin and the research

department in Nottingham, UK. The company has nearly 6,000 employees and is engaged in the research, manufacturing and marketing of enzymes, micro-organisms and ingredients for medicine. An important product is human albumin produced in yeast, and at the time when cooperation with our department was set up, Novozymes had already patented technology where drugs were attached to albumin. The purpose is to give medications longevity in the blood, and Novozymes has established relationships with several of the largest companies in the pharmaceutical industry, and tested some of their most important drugs in preclinical trials.

The new albumin variants are made fused to drugs, and each new drug coupled to an albumin variant is tested, initially in preclinical model animals, then clinically in patients; Novozymes enters into agreements with "Big Pharma" to assist them in testing their drugs.

There is now a series of alternative strategies for increasing the lifetime of drugs, and other biotechnological companies are promoting coupling to sugar groups or short chains of amino acids as well as encapsulation into micro- or nanoparticles to control release (9). Strategies where drugs indirectly connect to the body's own albumin are also in use (13). Novozymes is therefore marketing the concept of recombinant albumin-based half-life extension in competition with other companies. However, FcRn mediated rescue from intracellular degradation gives an additional effect, in particular when the albumin used for coupling has increased FcRn affinity and superlong half-life.

Inven2, the technology transfer office of the University of Oslo, and the Health Authorities in South and East Norway, negotiated the research agreement with Novozymes. Together with researchers from Novozymes, the Sandlie group then defined milestones, and Novozymes gained access to research results when Inven2 received milestone-payments from Novozymes.

The first milestones were linked to the study of the interface between the receptor and albumin, identification of albumin variants with particularly strong binding to the receptor, and last but not least, the study of how human albumin binds FcRn from other species, such as mouse and rat, typical laboratory animals used in preclinical testing.

It was agreed that Inven2 will receive payments when Novozymes has licenced patents that have resulted from the research collaboration, or sells albumin variants.

Commercialisation strategies

The licencing and further relationship with Novozymes represents only one of several possible choices in order to turn an invention into products. The Novozymes route represents an efficient way forward, in which a growing company that already has been building infrastructure in this technology space, decides to invest and progress the invention as one of their major projects.

Alternative commercialisation strategies are a one-off licence, which would exclude tight collaboration leading to further inventions and licences, or the establishment of a start-up company to take the technology all the way to market.

Research-based technology becomes industry

Ideally, the commercialisation of academic research should comprise a healthy mixture of new technology in the existing industry and technology to be "taken all the way" by a start-up. Most governments, including the Norwegian authorities, love the idea of the eager founder who is passionately devoted to her invention, who works inexhaustibly until she succeeds in creating a product, a large enterprise and lots of new jobs. Of course enthusiasm is a vital ingredient for innovation. More important however, is the actual data that shows that the invention works. Data is also important for existing industry to be willing to invest and develop it further. Industry will not simply "go and get the idea if it's good enough". Investments are based on data, risk evaluations and other practical assessments. A product that fits in with an existing company can in most cases be developed faster and has greater chances of entering the market than if the innovation is developed by a start-up company.

According to http://www.autm.net/FY2012_Licensing_Activity_Survey/12357.htm, more than 90% of all research-based innovations in the western world become products through existing industry, thereby assuring the future of existing companies.

When a company is established based on an idea from a research group, the group continue their research and come up with more ideas and patents. Such patents are usually licenced by, and added to the portfolio of the start-up, which in the meantime changes category from start-up to "existing industry". This is extremely positive and ensures a healthy development of many small companies. The best scientists in academic institutions should continue to do ground breaking research. They should not be distracted or delayed. Building industry from Norwegian research will mean that the best scientific groups continue their research while they recruit post-doctoral fellows and other scientific staff to pursue their innovative ideas. Normally, the scientific group rather than a contract laboratory is in the best position to obtain sufficient data to show whether or not an idea works, by repeated tests and experiments. Data that confirms the idea must be in place even before the most idealistic angel investors are willing to invest in the innovation. This is also the most efficient way for society to develop innovations, as it kills off ideas that are not worth further, and bigger, investment.

Whether or not an idea is suited for licencing as a new technology for existing industry or as the basis for the establishment of a new company is assessed by a thorough evaluation by technology transfer offices. Important factors in such assessments are: size of the new technology, maturation status, time to market, financial options and how well it would fit into the product line of an existing company.

Example:

In November 2013, an agreement for a potential blockbuster was reached between Inven2 and a large pharma company for the rights to develop a therapeutic for neuropathic pain based on epidermal growth factor receptor (EGFR) inhibitors. The pharma company already sells EGFR-inhibitors as chemotherapeutics and has a large patent portfolio on EGFR inhibitors. The agreement can potentially give billion NOK level funding to the Norwegian parties if a drug is successfully developed against neuropathic pain. The pharma company stands to earn a huge amount if the drug becomes a success.

Could a start-up company have taken this idea all the way to the market by investments of one billion NOK to gain a hundred back throughout the patent life period?

Let us look at what it would have taken to bring the idea to the market by a start-up:

400 mill NOK in capital for the company and clinical studies the first few years.
30+ employees with global competence in the area of EGFR inhibition and drug development.
In-licencing of patent rights on EGFR inhibitors from several pharma companies.

Although there is a growing health-care cluster in Norway, there are so many other opportunities for investment that it is not likely that such a significant amount of capital could be tied up in one invention that is to compete in a crowded space. Global drug development competence is critical to get the clinical indication and trials right the first time. There are many examples of small errors in clinical trial design that lead to years of wasted time. Capture of capital and staffing of the company with the right expertise would have taken 2–3 years, shortening the remaining time on the market with patent protection. In-licencing of immaterial rights would have been costly, as there are many patents covering the area.

The Big Pharma partner that Inven2 struck a deal with has the necessary in-house expertise to do the right clinical trials in a time-efficient manner. It also has the largest portion of the patent landscape of EGFR inhibitors. The company can develop the product 3–4 years faster than a start-up company, which could mean 1–2 billion NOK extra income for the Norwegian parties at the end of the patent protection period.

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Advances in Medical Technology both Strengthen and Challenge Health Care Organisation

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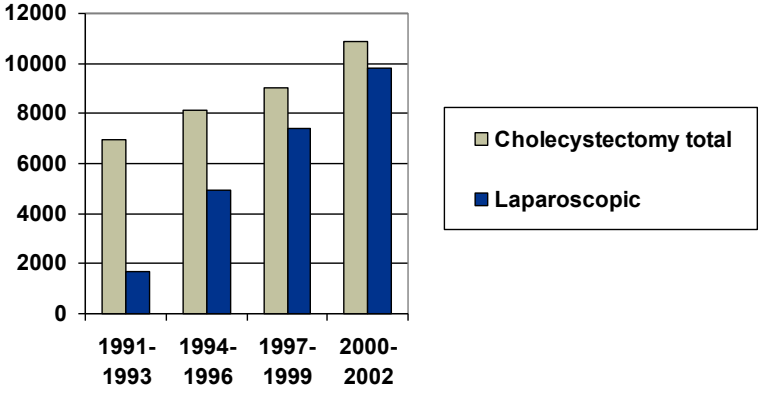
Advances in science and technology create many new possibilities and benefits for patient diagnostics and treatment. However, with these developments medicine becomes increasingly technology-dependent, which changes the range of skills needed. In the laboratories, the automation of analyses demands a structure and staff that ensure safe running of the machines. The interpretation and usage of gene sequencing require handling and processing of very large datasets. Knowledge of manual laboratory work has become less important than advanced informatics. In the radiology department, computerised systems like MR, CT and PET provide detailed and reliable patient diagnostics. Digital storage makes the images readily available to the physicians wherever they are, inside or outside the hospital. In the process, radiology departments become increasingly reliant upon technicians, physicists and computer scientists.

Laparoscopic, so-called key hole, surgery was first described and performed experimentally at the beginning of the 1800s, but was not a real option until the 1980s. The modern laparoscopic era was heralded by an appendectomy performed with the method in 1981 by the German gynaecologist Kurt Semm (1). In Norway, laparoscopic cholecystectomy (removal of the gall bladder) was introduced in 1990. Ten years later, 90 per

cent of all gall bladder surgery in Norway was performed laparoscopically (Figure 1) (2). Open surgery was no longer acceptable for this operation. Surgeons who had not learned the new method could no longer carry out the operation.

Figure 1. Gall bladder surgery in Norway 1990–2000 (2)



During the 1990s, gall bladder operations moved from open surgery to laparoscopic surgery.

In our department, endoscopic surgery on the oesophagus, adrenal glands and colon was introduced in 1996 (3), and laparoscopic resection of the pancreas and liver the year after (4). We performed the first laparoscopic prostatectomy in Norway in 1999. Today 60% of liver resections for colon metastasis are laparoscopic in our hospital. Minimal invasive graft harvesting in kidney donors is routine. Laparoscopic robotics-enhanced prostatectomy has become a gold standard. These changes in practices from open surgery with simple technology to minimal invasive surgery with expensive equipment represent a major challenge to hospital finances, as equipment expenses in the operation room have increased significantly. On the other hand, the procedures lead to earlier discharge from hospital and reduced convalescence, which represent cost savings.

Political impact of medical technology

The impact of technology dependency in health care, however, is more than just increased equipment costs and shorter hospital stays. It forces new ways of organising health care. Robotics-enhanced laparoscopic surgery

for prostate cancer, which is now routine in Norway as in most European countries, exemplifies some of the challenges of introducing advanced and expensive technology for a common surgical procedure. The cost-effectiveness of robotics-enhanced prostate surgery is still not fully documented (5).

Investment in the robotic equipment represents a major cost to any hospital; in Norway currently three million EUR. In addition, the disposables are more expensive than in open surgery. To be safe, robotic-enhanced surgery requires special training and skills not only for the surgeon, but also for the whole team. And for a team to maintain their competence, they require a sufficient volume of operations.

In Norway, most urological departments used to perform prostatectomies for early stage prostate cancers. Few of them carried out more than 20 operations per year. When the first hospital acquired a robotics-enhanced system, which involved purchasing expensive equipment and training doctors and nurses in the technique, they started performing 10–20 operations a week. The costly investment in robotic technology inevitably led to centralisation of prostate surgery, but this occurred without regional discussion or political decisions.

As more centres invested in robotics equipment, the indications for prostatectomy changed. There is now a discussion whether too many patients are offered prostatectomy; even at experienced centres, impotence and incontinence are common complications.

In Norway, some communities in their struggle to keep their local hospitals have used procurement of robotic technology. In the south of Norway, the hospitals of two nearby cities, Kristiansand and Arendal, merged into one health enterprise. Both hospitals had a urological department. In 2011, the management decided to concentrate all prostate surgery at Kristiansand, but within one week a company in Arendal donated a da Vinci system to the local hospital, an offer the management could not decline; Arendal became the prostate surgery centre.

In one small town in the middle of Norway, Orkdal, the local hospital was under threat of closure in 2012. A local non-governmental organisation then donated a da Vinci system in the hope that the hospital would become a regional centre for prostate surgery. The strategy worked. The local health

authority could not decline the gift and decided to establish Orkdal as the prostate centre for mid-Norway, and the threat of closure disappeared (6).

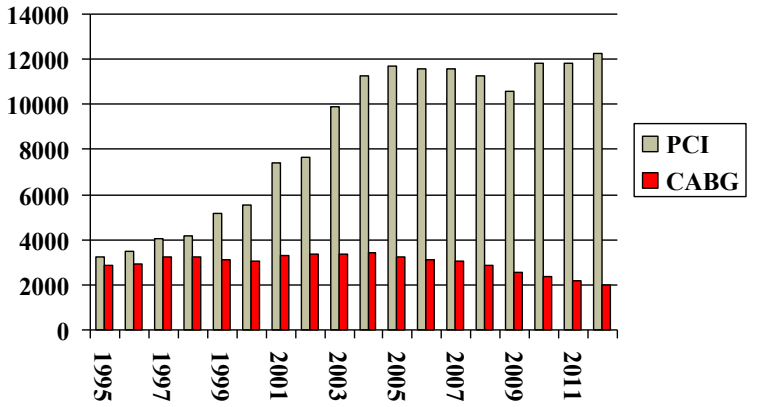
These two examples demonstrate that advanced medical equipment is a powerful political tool at both a local and a regional level, despite the fact that all the hospitals in question are state-owned. In both the cited cases the authorities had to reverse their decisions due to the donations.

Changing practices

The evolution of medical procedures also has major impact on how a hospital is run. The whole approach to treating some conditions can change in response to technological advances, challenging the existing hospital structure and causing rivalry and turf battles between medical specialities. The development of cardiovascular treatment is a good example. Since the first publication of percutaneous coronary intervention (PCI) by Andreas Grüntzig in 1979 (9), PCI has become one of the most frequently performed procedures in hospital. Before the advent of PCI, open coronary surgery was the most effective cure for coronary arteriosclerosis. In Norway, PCI was introduced in 1981, and the number of procedures is still increasing. In 2012, 12,235 PCIs were performed, whereas coronary surgery peaked in 2004 with 3,430 operations. Since then the number of surgical procedures has diminished every year, to 1,968 cases in 2012 (Figure 2). The trend we have experienced in Norway is global; during recent decades, the non-medicinal treatment for coronary disease gradually was transferred from the surgeons to the cardiologists. This caused some consternation among cardiothoracic surgeons. Since 2000, catheter-based treatment of the most common congenital cardiac disorders like atrial and ventricular septal defects has become standard, transferring also these patients to the cardiologists. Eventually, transcutaneous aortic valve replacement was introduced as an alternative to open aortic valve replacement. This has limited the need for standard cardiac surgery, with consequences for recruitment and training. There is a growing awareness among both vascular and cardiac surgeons that they will have to change their training curricula if they want to stay in business.

However, catheter-based valve replacement is not always a straightforward interventional procedure. As the interventional procedures became

Figure 2. Treatment of coronary disease in Norway 1995–2012 (9)



In Norway coronary surgery peaked at 34,030 operations in 2004. Since then the number has steadily decreased to 1,968 patients in 2012. Percutaneous coronary intervention reached its peak in 2012 with 12,235 procedures.

more advanced, it became evident that many patients could benefit from having both intervention and surgery simultaneously. The possibility to convert an interventional procedure into a surgical procedure, or plan a combination of the two techniques increases patient safety and the possibility to perform treatment with minimal trauma to the patient. Thus, several centres like our own department have built surgical suites with integrated advanced angiographic equipment. In these hybrid suites, surgeons and cardiologists often work together. Treatment of patients with cardiac and vascular disease today requires doctors with both interventional and surgical skills.

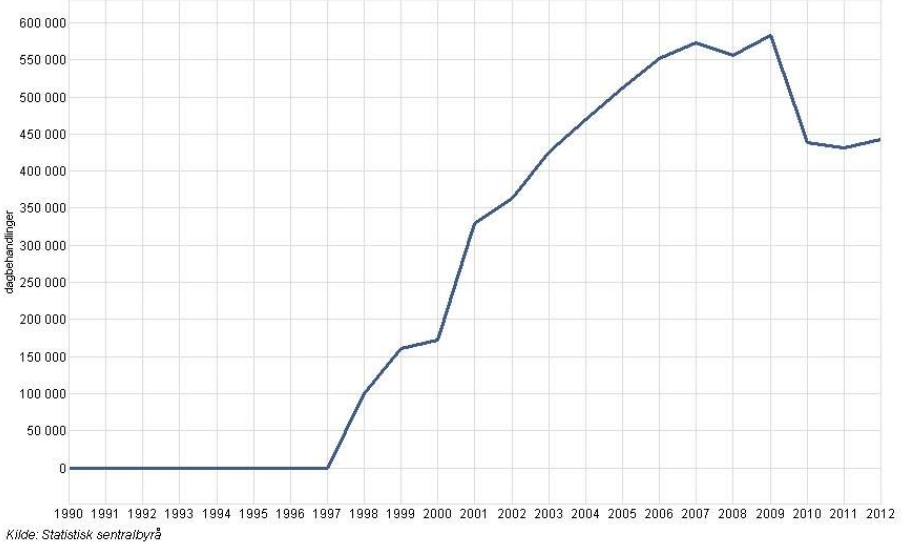
The development towards more technology-dependent procedures also challenges the principle of equality in health care. Like laparoscopic and robotics-assisted surgery, the endovascular techniques require expensive equipment and training, and a high volume of procedures per centre to be safe and cost-effective. The centralisation of procedures that we have seen in prostate surgery seems to be a general consequence of the technology dependence. In Norway, hospitals with a low volume of procedures tend to choose standard open surgery for aortic aneurysms, hysterectomies for uterine fibromas, liver surgery, pancreatic surgery and renal surgery, while in centres with a higher volume the patients often are offered a minimally

invasive technique. In Norway all patients can choose the hospital where they want to be treated, however the majority of patients tend to choose the closest hospital, or the hospital recommended by their doctor. This may be due to lack of knowledge of the treatment options, or that they feel safer close to home. To an increasing degree, the type of treatment will depend on where the patient lives.

Shorter stay in hospital

As the minimal invasive techniques allow shorter stays in hospital, so-called day care surgery was introduced in 1990. Initially only a few hospitals offered this service, but after the introduction of activity-based funding of public hospitals in 1997 the number of day care patients increased rapidly to almost 600,000 a year in 2007. In 2009 the Norwegian health authorities introduced differentiated payment for in-patients and day care patients, leading to a drop in day care patients to 439,085 in 2010. (Figure 3). In the

Figure 3. Day care patients in somatic hospitals in Norway. Source: Statistics Norway (10)



Day care patients in somatic hospitals increased significantly when activity-based funding was introduced in 1997. In 2009 the health authorities introduced differentiated payment to hospitals for in-patients and day care patients, and the number of day care patients dropped.

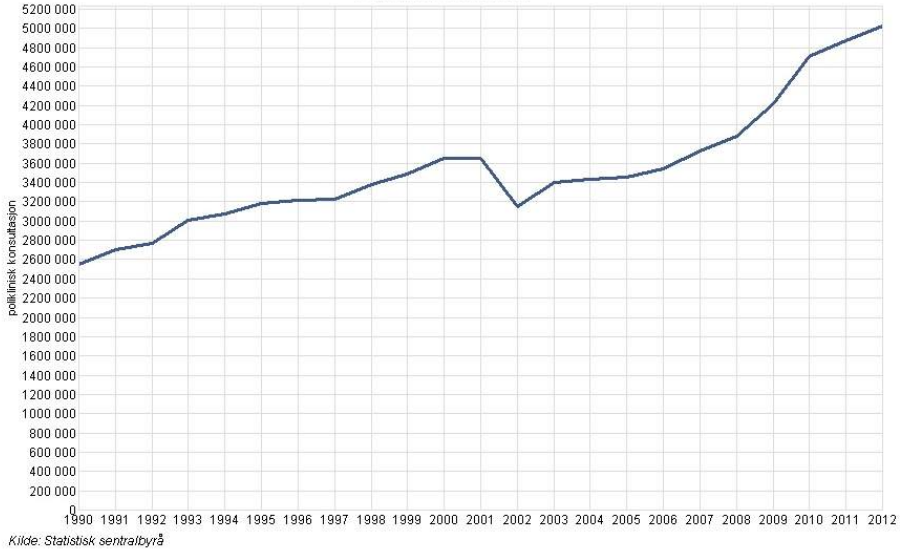
same period the number of out-patients increased steadily (Figure 4) (10). This trend implies that the patients tend to have shorter contact with specialised care. Gradually the responsibility for follow-up, rehabilitation and nursing has been transferred from the hospitals to the primary and community healthcare. The main challenge to Norwegian health care today is thus the communication and collaboration between specialised and primary health care units.

The corporate culture challenges the artisan culture

Inside the hospital, the main challenge is the transition and clash between the new public management culture and the traditional medical professional culture, as the two cultures contain completely different sets of values.

The medical professional culture is basically an artisan's culture and the medical professional's identity is closely linked to their artisan identity. This identity and its values are challenged by the transition of the hospitals from organisations with little technology where the medical artisan was in the centre, towards technology-dependent organisations where cost control

Figure 4. Out-patients in somatic hospitals in Norway, Source: Statistics Norway (10)



Out-patients in somatic hospitals increased steadily and has compensated for the drop-in day care patients from 2009.

and detailed financial planning are key elements. In addition, other specialists with a long university background like physicists, engineers, mathematicians and pharmacologists become increasingly important for the running of the hospitals.

Ownership of a method

In the traditional artisan workshop, the owner of every procedure is the master craftsman and this ownership is protected collectively by the artisan's guild as a common asset. The artisan will not share his secrets outside the guild as therein lies his power. In the corporate culture, the company management has the ownership to all procedures. The CEO with the approval of the board can decide to stop a procedure or outsource it. The company's financial position is the overriding factor for such decisions. When corporate decision-making is applied in a hospital context, medical arguments will sometimes take second place. The introduction in 2001 of public management in all the state hospitals in Norway resulted in a sense among medical professionals that their power had been reduced and their knowledge asset potentially undervalued.

Development and research

In the artisan culture, product development is an integrated part of the production. The artisan develops his skills and continuously adopts new techniques and methods. This is the way all new procedures were introduced in hospitals. The doctors did not consciously differ between method development and routine practice. The weakness of this method of working became obvious when we introduced laparoscopic surgery in the late eighties and early nineties. We did not design a protocol or a scientific framework before we started, but purchased the equipment, trained at courses often arranged by the producers of the equipment, and started practicing on patients without informing them that they were part of a huge development programme. In Norway, several patients suffered from severe complications after surgery that when performed openly was considered quite safe. The patients paid for the learning curve.

Expensive technology-dependent methods that demand a team of skilled professionals often require a structured introduction. In Norway, since 2013,

the health authorities have therefore required a structured and critical evaluation of the existing documentation of the technology, a so-called Health Technology Assessment, before hospitals introduce new technologies in clinical practice (11). If there are gaps in the documentation, the hospital has to design a study to monitor the introduction of the method. My own department, the Intervention Centre, was established with advanced surgical suites integrated with angiographic radiological equipment and MRI to be a development department for new methods. Clinicians from other departments and hospitals are invited to use the Centre for development and testing of new methods together with the Centre's staff before introducing them in routine practice (12, 13). This is analogous to the industrial approach, where there is no room for improvisation in the production line and the development department is separated from the production area. The standardisation of production is essential both for quality and cost control in the company. In the development department, design, material, performance and durability are tested. Then a plan is made of what tools will be needed, what skills the team performing the production need to have, and the production costs and price of the product. As advanced technology-dependent methods are introduced, hospitals will have to adopt the industrial R&D strategy.

Knowledge transfer and training

In the artisan culture, the training is based on the master-apprentice principle. This implies learning through personal instruction, with formal course training less important. The apprentice gets his training under supervision by the master. The aim and advantage of this way of training is that it gives a broad overview of the field and the future master learns the resilience needed to cope with unforeseen problems.

Industrial, technology-based production needs specialists with short and specific training to run the technology. The individual workers do not need a broad overview as they will be working in a team and the team will have the overview. As in industry, the worker is going to work in a standardised system, and does not need the resilience of the artisan.

Thus, in corporate thinking, long and wide-ranging training is both uneconomic and unnecessary. The trend in medicine is also to move towards shorter general training for specialists. Several countries have moved away

from the training of general surgeons and internists and start directly with more branched specialisation like neurosurgery, orthopaedics, cardiothoracic surgery, cardiology etc. Hospitals that offer a complete service 24 hours then need to have several teams of specialists on a duty rota.

Collaboration

Each artisan is a specialist in his field. If several artisans are needed on the same project, co-ordination is required. To ensure collaboration in complex building projects an entrepreneur will co-ordinate the different artisans. The co-ordination does not come by itself as the artisans mainly communicate with colleagues of the same guild.

The tradition in hospitals has been for the artisan culture to set the rules regarding how the hospitals are organised. Each speciality would build their own organisation, clinic or department. Patients referred to that department get treatment for the disease if it falls within the boundary of the specific speciality. However, the patient will invariably need services from other departments in the hospital, and to co-ordinate the waiting lists and maintain smooth collaboration the hospitals have to hire patient co-ordinators. At our hospital, the co-ordinator function is relatively new. Previously a patient typically would have to visit the hospital several times for appointments in different departments with the specialists they needed to see. The modern industrial ideal is so-called lean thinking, where cross-disciplinary collaboration is a cornerstone.

Quality and decisions

The experienced artisan may be able to cope with all unforeseen problems within his field. Even if the work is not standardised, the level of quality may be high due to the experience and pride he puts in his work. The job is part of his identity.

On the other hand, there is no documentation of an artisan's skills; the only way to quality assess an artisan is to get references on how he has performed before. The quality management in an artisan organisation, like for example a hospital department, is based on resilience. The teams on duty will cope with all unforeseen events, and they will combine their long experience in solving the problem.

In the corporate culture, quality and safety are based on standardisation of procedures and the use of quality management systems. If you can identify every detail of a procedure and ensure that the procedures are being followed, you can also foresee the result. The aim is to create predictability in the product. In Europe the CE mark is a mandatory conformity marking for certain products sold within the European Economic Area. CE marking signifies that the product conforms with all EC directives that apply to it. The producer has to be able to document that the development and production of the product conforms with the directives.

In hospitals, we have during the last decades introduced similar quality systems, so-called evidence-based medicine. This type of standardised quality care works well in predictable situations. The challenge for health care is to still maintain the resilience of the craft culture (14). The hospital situation where acute and unforeseen events occur all the time is not easy to standardise. On the other hand, standardisation is a condition for day care surgery, where the hospital staff manage quite well. Evidence-based health care is now gaining more impact in hospitals. All over the western world they are introducing quality management systems. However, many medical specialists claim that standardised medicine underestimates the complexity of clinical work. If we do not maintain the resilience and ability to improvise inherent in the artisan culture, patient safety may be at risk, particularly in emergencies.

Value

Whereas the value of an artisan product depends on the way it is produced, that is by an artisan, the value of an industrial product lies in its brand and specifications, the customer does not need to know the identity of the worker as long as the product is produced in a standardised way. In healthcare we have to question whether the patient wants an artisan product or a standardised industrial product. The answer in most cases is that the patients want both. They want the predictability of an "industrial" product – they want to know how long they will have to stay in hospital, how long they will be away from work etc. On the other hand they want the personal contact with the surgeon and staff involved in the treatment.

The challenge of combining two cultures

The increasing dependence upon advanced technologies, and thereby a complex organisational structure, requires corporate management. At the same time, the values of traditional medical artisan thinking are important for coping with complex situations that can arise during treatment of patients (14).

In Norway, the health authorities' way of coping with technology-based medicine has been to merge small hospitals into major corporations, to introduce quality management systems and to take control of the decisions about where and how treatment for specific diseases is made.

These reforms have been met with severe criticism by several medical professionals, claiming that the personal handling of the patient is getting lost, and often rightly pointing to the fact that it is necessary for the management of a hospital to have some knowledge of the medical challenges.

As medical care is getting more and more dependent on advanced technologies, the contradiction between the artisan and the corporate cultures is becoming the most important challenge facing health care management. It is probably more important than the contradictions between different hospitals, between different specialities or between the different professions in hospital.

To make modern health care safe and financially affordable a successful merger of the values of the artisan culture and the corporate structure is mandatory.

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Author CVs

Bent Høie is the Minister of Health and Care Services, responsible for government policy related to hospitals, municipal health-care services, preventive measures, psychiatric health and drug addiction.

In 1991 Høie took the foundation course in Law at Bergen University before studying Hotel Administration for two years. By 1990 he had already become chair of the Young Conservatives in Rogaland county, and from 1993 to 1995 was a member of the national executive. He held various Conservative Party posts in Rogaland and Stavanger, with the Chair in Stavanger 2000–2002. He sat on local government councils in the same region from 1991 to 2003.

Høie was elected to the Storting (Parliament) in 2001 as a Member for Rogaland, after being deputy representative/representative 1997–2001. Between 2001 and 2009 he served consecutively on three parliamentary standing committees: for Energy and the Environment, Health and Social Affairs, and Local Government and Public Administration. In 2009 Høie became Chair of the Standing Committee on Health and Care Services, a position he held until 2013 when he was appointed Minister.

From 2000 to 2006 Høie was also Board Chair of the Dyslexia Research Foundation.

Kristin Braa has been a Professor at the Department of Informatics at the University of Oslo since she returned from Telenor in 2009. There she was Research Director and she established and headed the Telenor Research & Innovation Centre, taking care of research and innovation in Telenor's Asian operations. She is currently heading the Health Information Systems Programme (HISP) network, initiated at the University of Oslo in 1994.

HISP is a global action research network which is responsible for the development of the open source based District Health Information Software (DHIS 2). DHIS 2 is developed, customised and used for reporting, analysis and dissemination of health data for many health programmes. It has been implemented in over 40 countries in Africa and Asia including 12 states in India. The DHIS 2 mobile program is developing a suite of mobile solutions for low resource settings, using mobile phones to collect data as well as tracking beneficiaries on maternal and child health in an integrated manner. This is of particular relevance in places without computers and where the only Internet is mobile Internet.

Petter Nielsen holds a PhD in informatics from the University of Oslo. Working for 10 years as a researcher and business developer in the international telecommunication industry, he is currently Associate Professor at the University of Oslo. His research interests relate to the design and implementation of large scale and complex information infrastructures, with a particular focus on architecture, control and innovation. His empirical research ranges from mobile content services and the mobile Internet in Northern Europe and Asia to the emerging field of mHealth in developing countries.

Ola Hodne Titlestad is a senior engineer at the Department of Informatics at the University of Oslo. The last 12 years he has been actively engaged in the Health Information Systems Programme (HISP) and supported countries in implementing the open-source DHIS 2 software (**www.dhis2.org**). As part of the HISP network Ola has worked extensively in Africa and Asia and provided technical support to ministries of health on information systems strengthening and capacity building. In 2009–2010 he worked at the Health Metrics Network, at WHO in Geneva.

Jan Terje Andersen is a researcher at the Oslo University Hospital, and group leader since January 2014. He has a PhD in molecular biology and has held postdoctoral positions with Professor Inger Sandlie. He is co-inventor on patents that describe the production and use of modified antibodies and albumin.

Ole Kristian Hjelstuen is CEO of Inven2, an innovation company of 27 highly skilled personnel with broad scientific and extensive commercial experience. Inven2 is approaching the top league in Europe with 38 commercialisations and a major Big Pharma deal in 2013. Ole Kristian has 23 years experience from the pharmaceutical industry, the last 9 years as Director and Executive of GE Healthcare. He also holds a position as Professor in Pharmaceutical Sciences at the University of Tromsø.

Inger Sandlie is Professor of Molecular Biology and Deputy Director of the Centre for Immune Regulation, University of Oslo. She has a PhD from the University of Bergen and has held postdoctoral positions at Johns Hopkins University, USA and the Norwegian Cancer Hospital. She heads an active research group and is co-inventor of patents that describe the production and use of modified antibodies and albumin. Furthermore, she is co-founder of two biotechnology companies, Vaccibody A/S and Nextera A/S, and has extensive research collaboration with Novozymes A/S. In 2011, she received the first Innovation Prize awarded by the University of Oslo. She is a member of the Norwegian Academy of Science and Letters.

Erik Fosse, MD, Ph.D., is a board certified specialist in general surgery and cardiothoracic surgery. He is Professor of Surgery at the University of Oslo and Director of the Intervention Centre, which is a research and development department at Oslo University Hospital www.ivs.no. The Centre is a toolbox for the development of new advanced medical procedures. Erik Fosse is also Director General of NORWAC, a humanitarian organisation www.norwac.no, and previous Chair of the Human Factors and Medicine panel of the Science and Technology Organization in NATO. Erik Fosse is author or co-author of more than 200 peer-reviewed scientific papers, and has written several books on cardiac and trauma surgery. Erik Fosse has been awarded several prizes for his humanitarian and scientific work, and in 2013 he was made Commander of the Royal Norwegian Order of St. Olav.