Model Driven Paediatric European Digital Repository

Call identifier: FP7-ICT-2011-9 - Grant agreement no: 600932

Thematic Priority: ICT - ICT-2011.5.2: Virtual Physiological Human

Deliverable 19.1

Health Technology Assessment (HTA) - Evaluation Approach & Framework

Due date of delivery: 28-02-2014

Actual submission date:

Start of the project: 1st March 2013

Ending Date: 28th February 2017

Partner responsible for this deliverable: EMP

Version: 03

Dissemination Level: Reserved

Document Classification

Title	***Health Technology Assessment (HTA) - Evaluation Approach & Framework***
Deliverable	19.1
Reporting Period	1
Authors	EMP
Work Package	WP19
Security	R
Nature	RE
Keyword(s)	Health Technology Assessment, HTA, framework, approach, scenario, clinical pathway

Document History

Name	Remark	Version	Date
Karl Stroetmann		1.1	20th January 2014
Karl Stroetmann		1.2	10th February 2014
Karl Stroetmann		1.3	28th February 2014

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Nature of this Deliverable

This Deliverable relates to Task 19.1 and others of WP 19 Exploitation, HTA, and Medical Device Conformity of the MD-Paedigree Project.

1. Executive Summary

Health Technology Assessment (HTA) is a multi-disciplinary field of policy analysis that examines the medical, economic, social, and ethical implications of the incremental value, diffusion, and use of a medical technology in healthcare. As VPH technologies usually do not constitute an incremental, often marginal improvement of health technologies, but rather a leap forward towards more predictive, personalized, integrative, and efficient healthcare provision, a critical reflection of HTA approaches is undertaken. This includes reviewing and developing a VPH-focused evaluation approach and meaningful indicator development.

The overall *goal* of the tasks in *WP 19 Exploitation, HTA, and Medical Device Conformity* is to contribute from a socio-economic and commercial perspective towards making computer-based models and simulations readily available at the points of care and to researchers. This involves preparing an appropriate analytical evaluation framework and undertaking groundwork for exploring market access, including meeting regulatory requirements of medical products. This also includes exploring health system and business opportunities.

For the first task and this deliverable, these specific objectives are pursued:

- Review HTA research & achievements and prepare for a dynamic VPH approach, including
  - ✓ Critically revisiting conventional health technology assessment procedures and approaches
  - ✓ Developing upon and adapting in the VPH and other contexts proven approaches, methods, and tools
  - ✓ Establishing a set of meaningful criteria and their measurement process that are robust to demonstrate socio-economic benefit/cost impacts.
- Prepare for clinical impact assessment and cost-benefit scenarios.

Chapter 3 briefly analyses core HTA methodological challenges with respect to evaluating VPH technologies, establishes a more precise, well-defined terminological framework for generic HTA work as a base for further discussions, and briefly explores the role of HTA in policy decision-making processes and implementation considerations.

Next, to progress towards an HTA approach which is amendable towards the specific requirements of the VPH modelling and computer aided medicine context, chapter 4 explores a life-cycle approach towards what has been called Technology Readiness Level (TRL), or, as we prefer to name it, the respective RTD workflow stage of the technology to be assessed. Specific verification, validation and evaluation approaches compatible to the respective stage reached are identified. Next, decision-related impact and assessment levels are briefly explored, followed by a discussion of the temporal dimension of assessments.

In a dynamic context, dependent on the development stage of the technology, certain impacts may already undergo concrete assessment like the accuracy of a model, but its future health impact may only be forecast and estimated at a rough level of precision. In such a dynamic context as the model development activities of MD-Paedigree, it will be important to estimate and assess the likely

- further path of learning of the system implemented, like its increasing accuracy of predictions of likely disease progression for a particular patient as more data from past experience emerge, of the likely impact of treatment options, and the like,
- the rate and shape of the diffusion curve over time
- the temporal end point of the diffusion saturation level across healthcare provider organisations.

These are aspects of core relevance when estimating the likely long-term impact of VPH technologies – aspects which are neglected in conventional HTA assessments.

The final goal of the planned impact assessment is to estimate a high-level generic benefit-cost scenario for exploring the potential clinical and socio-economic impact of MD-Paedigree applications. Based on a discussion of scenario approaches in general, in the specific context of VPH technologies so-called explorative scenarios are proposed to be applied in the MD-Paedigree context. This type of scenario reflects both the specific purpose of our exercise and the speculative, uncertain nature of the overall scenario situation.

Next, key steps towards developing such scenarios in a generic VPH context are presented, as well as core variables and considerations are outlined to be applied to deliver the results required. Initially central concerns and key issues of potential users of the scenarios to be developed are identified and explored. Such users will come from the health policy community and from those individuals developing and supporting eInfra- and eInfo-structures to allow our health systems to better meet urgent health challenges. Next, those driving forces that are likely to have the most important influence on these central concerns of the future are discussed. From this a generic scenario plot is derived identifying the two critical factors of the central themes of the scenarios deemed most relevant. This is complemented by a brief exploration of key aspects of a socio-economic impact assessment, with a particular focus on clinical impacts. All of this is then reflected for elaborating the basic scenario logic into full-fledged scenarios. The results obtained strongly suggest in future work to pursue the further development and exploration of just two of the potential four scenarios, namely to:

A) Focus on a scenario driven by ICT/VPH technology progress only

B) Focus on an alternative scenario moving towards integrated service provision and investment in VPH tools and services

These scenarios to be built and assessed with respect to their probable benefits and costs in further tasks of WP19 will illustrate how through newly developed clinical pathways the transformation of bio-computational modelling and VPH technologies into a future patient flow will supplement and improve the current management of the specific diseases targeted by MD-Paedigree. The VPH technology assessment framework developed and proposed in this deliverable will force many of the implicit assumptions behind such developments to lay bare. Since the assessment perspective is to develop concrete clinical scenarios, the further work on the MD-Paedigree technologies will clearly benefit from a more focused alignment towards producing results that matter within the context of deployable, routine clinical applications.

2. Background, goal and objectives

This introductory chapter will briefly explore the background and global context of the VPH Initiative and computer aided medicine. It reports on the overriding goal of the work to be presented and to be undertaken further on in WP 19, and states concrete objectives of the tasks to be performed.

2.1. Background

Health Technology Assessment (HTA) is a multi-disciplinary field of policy analysis that examines the medical, economic, social, and ethical implications of the incremental value, diffusion, and use of a medical technology in healthcare. As VPH technologies usually do not constitute an incremental, often marginal improvement of health technologies, but rather a leap forward towards more predictive, personalized, integrative, and efficient healthcare provision, a critical reflection of HTA approaches is undertaken. This includes reviewing and developing a VPH-focused evaluation approach and meaningful indicator development.

All of this has to be seen and put into the context of the global VPH and Physiome Projects. Globally, there is a growing interest for computational technologies in the area of medicine. Whereas ICT already plays a decisive role in medical informatics, bioinformatics or telemedicine, the use of ICT as a support for prevention, screening, diagnosis, treatment, and monitoring in computer aided medicine remains limited. Yet it is by now evident that this is the area of medical technology most likely to revolutionize the practice of medicine. Computer models that simulate physiopathological processes can be employed to take clinical decisions on the basis of “what-if” analyses (predictive medicine), to tailor the delivery of care to the specific needs of individual patients (personalized medicine), and to explore pathological scenarios for systemic interactions between multiple physiological processes (integrative medicine).

In Europe, the global framework of methods and technologies that will permit the delivery of a predictive, personalized, and integrative medicine has been developed under the name of Virtual Physiological Human (VPH). The VPH is a framework of methods and technologies that once fully established will make possible the investigation of the human body as a whole. Started in Europe in 2005 it rapidly grew to become one of the research priorities of the European Union Seventh Framework Research Program. In the USA, VPH-type research is funded, beyond the National Institutes for Health (NIH), by ten federal agencies that participate in the Interagency Modelling and Analysis Group’s (IMAG) Multi-Scale Modelling (MSM) initiative established in 2004, which brings together over 80 investigators. One outgrowth of the MSM initiative that specifically encouraged the extension of multi-scale modelling to “higher scales” of biological organization and applications to clinical translation was the NIH program first announced in 2008 on “Predictive Multiscale Models of the Physiome in Health and Disease”. The goal of this solicitation was to move the field of biomedical computational modelling forward through the development of more realistic and predictive models of health and disease.

These initiatives have been marked by a demand for measurable evidence that such complex technology is actually worth the cost. This concerns how to quantitatively assess such technologies in terms of safety, efficacy, and socio-economic impact. And how the transformatory impact on clinical guidelines can be assessed.

2.2. Goal

The overall goal of the tasks in WP 19 Exploitation, HTA, and Medical Device Conformity is to contribute from a socio-economic and commercial perspective towards making models and simulations readily available at the points of care and to researchers. This involves preparing an appropriate analytical evaluation framework

and undertaking groundwork for exploring market access, including meeting regulatory requirements of medical products. This also includes exploring health system and business opportunities.

2.3. Objectives

For the first task and this deliverable, these specific objectives need to be pursued:

- Review HTA research & achievements and prepare for a dynamic VPH approach, including
  - ✓ Critically revisiting conventional health technology assessment procedures and approaches
  - ✓ Developing upon and adapting in the VPH and other contexts proven approaches, methods, and tools
  - ✓ Establishing a set of meaningful criteria and their measurement process that are robust to demonstrate socio-economic benefit/cost impacts.
- Prepare for clinical impact assessment and cost-benefit scenarios.

2.4. What follows

In chapter 3, a generic HTA framework is presented, starting from a discussion of methodological challenges, then providing a more detailed definition of Health Technology Assessment, including a review of socio-economic concepts as applied in this context – issues which are of particular relevance for future work. When developing VPH technologies and HTA approaches to be applied, it is regarded as particularly relevant to differentiate across the RTD workflow stages of the technology development, and identify appropriate assessment approaches which correspond to the specific verification, validation and evaluation needs of the respective stage.

In the VPH context with its longer term perspective till widespread clinical diffusion has been achieved, the dynamic, temporal dimension and its reflection in the approach to be chosen is of particular importance.

It follows a concise discussion of measuring benefits and costs, including the operationalisation of measures and measurement tools.

Finally, the methodology of generic impact scenario approaches is explored at some detail because this will become a core base for future work as well. It discusses various aspects, dimensions and approaches for scenarios of future healthcare delivery, and identifies key health system challenges as well as central factors and driving forces of future scenarios.

3. Generic HTA Framework

This chapter analyses briefly core HTA methodological challenges with respect to VPH technologies, establishes a more precise, well-defined terminological framework for generic HTA work as a base for further discussions, and briefly explores the role of HTA in policy decision-making processes and implementation considerations. Specific VPH aspects will then be discussed and determined in the next chapter.

3.1. Methodological challenges

Health Technology Assessment (HTA) is a multi-disciplinary field of policy analysis that examines the medical, economic, social and/or ethical implications of the incremental value, diffusion, and use of a medical technology in healthcare provision. Conventional (HTA) methods

- look at existing, "mature" technology, provide information on consequences and implications of use (and are accordingly not used as an aid in research guidance, product or service development)
- are, as a consequence, not sufficient for complex multiscale simulation technologies.

On the other hand, the impact of simulation models and computer aided medicine on clinical decision making and practice may be far reaching, causing organisational, management, cultural – disruptive – impacts which have a potential to

- revolutionize prevention and diagnosis
- predict disease progression and outcomes related to treatment options
- generate new knowledge from patient and other health data (learning, adaptive decision support systems, which are different from conventional, static decision-support systems).

To move towards a better understanding of the role of HTA and to further develop the HTA concept to better suit VPH-specific purposes, the following subsection provides for a more comprehensive, detailed definition of terms applied and used in our further HTA work.

3.2. Defining Health Technology Assessment

3.2.1. Basic definitions

In developing upon commonly used health technology assessment (HTA) definitions[1], we understand HTA to mean

> ***the transparent, purpose-driven assessment - based on explicit assumptions - of the impact of newly developing or already developed health technologies on issues of relevance for health policy decision making.***

In more detail, the following Table 1 summarises what this refers to:

[1] Goodmann, C. S. (2004). HTA 101 Introduction to Health Technology Assessment, Falls Church, VA.

TABLE 1: BASIC DEFINITIONS OF HTA TERMS

Term	Definition
Transparency/ Falsifiability	Scientific method-based, therefore transparent, making assumptions explicit, and in principle repeatable and falsifiable by others, i.e. open to scrutiny by and in need of validation by the (HTA) community.
Purpose-driven; issues of relevance for health policy decisions	Any HTA exercise will always have a distinct purpose, which usually will be informing decision making in the context of a specific health policy issue for a specific stakeholder, several stakeholders, a stakeholder group or groups of stakeholders. Policy is understood to also concern issues at the concrete implementation level of an individual person or organisation, not only at the societal level. The pending decision may be directly related to health or indirectly, like a technology development intended to be of benefit for health.
Assessment	In principle, the assessment may concern • only the technology under consideration. However, given the fact that health service provision constitutes one of the oldest services we have (since the early years of Egyptian culture), and demonstrates a certain maturity, it is common practice and will also be assumed here that usually the assessment will concern • two (or more) competing technologies. Assessment feasibility alludes to the availability of relevant evidence, time and resources required to complete a meaningful assessment.
Impact	To observe an impact, there must exist a direct or indirect causal relationship between an input (research effort; medical intervention; ...), and an output (new simulation model; improvement of health; ...) or result, facilitated by the technology and its property(ies), e.g. usability. One should distinguish • intended impacts • unintended impacts. Further, one should distinguish between • primary impact(s) like on the health of an individual person, and • secondary (tertiary, ...) impacts like on the labour market or tax income of the government when due to better health a person is longer employed, etc.
Newly developing or already developed	The health policy issue may concern not only an already existing, usually proven technology (as with conventional HTA), but also a technology on the drawing board or at the research and/or development stage.

Health	According to the WHO, "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."[2]
Technology	Technology means "the application of scientific knowledge for practical purposes, especially in industry."[3] Three basic types of technology - which in reality mark end-points of scales rather than clearly distinct entities - need to be distinguished: • *Simple* technologies, like a drug containing only one active ingredient, which may not disturb or change established clinical processes • *complex* technologies which may combine different technical components, requiring more complex assessment methods, and • *transformative* technologies that may lead to a disruptive change in clinical practice.

Given this basic definition and initial explication of the meaning of HTA, we will now further explore this concept and discuss briefly key dimensions, thereby explicating this further and helping us to operationalise the various HTA dimensions in a way amenable to application in the MD-Paedigree and other dynamic contexts.

3.2.2.Common HTA assessment perspectives

Commonly, the following HTA assessment perspectives can be distinguished, which will depend on the specific decision support context within which an HTA study is being undertaken:

a) Assessment of effectiveness and safety of technology

- Clinical benefits, clinical effectiveness, generalisability of results for healthcare provision,
- Risk (with patient safety being a judgement of the acceptability of risk)

b) Assessment of organisational, legal, ethical, and socio-cultural impacts

- Organisational implications (impacts on structures, processes; groups of stakeholders, acceptability)
- legal (legal frameworks), ethical, socio-cultural implications

c) Assessment of socio-economic consequences

- Socio-economic analysis, e.g. cost-effectiveness, benefit-cost analysis
- Return-on-investment analysis, business case development

[2] Preamble to the Constitution of the World Health Organization as adopted by the International Health Conference, New York, 19-22 June, 1946; signed on 22 July 1946 by the representatives of 61 States (Official Records of the World Health Organization, no. 2, p. 100) and entered into force on 7 April 1948.
[3] See Oxford Dictionary at http://www.oxforddictionaries.com/definition/english/technology

3.2.3.Further generic definitions of HTA socio-economic concepts

As a focus of future work will be on the socio-economic impact of the newly developing VPH technologies, and also to support exploitation considerations and business planning, some core concepts in this context are further explored and identified in the following Table 2:

TABLE 2: DEFINITIONS OF HTA SOCIO-ECONOMIC CONCEPTS

Socio-economic impact:	The potential aspects of impact for each stakeholder – benefits and costs to citizens, healthcare professionals and healthcare providers, and third party payers. Costs encompass negative impact, whereas benefits reflect positive impacts. The resulting quantitative measures, although presented in Euros, do not reflect financial flows or only the economic aspects of impact. They are merely a comparable representation, i.e. an index, of the impact, including economic as well as social, cultural, and organisational aspects.
Microeconomic impact:	a) Refers to costs, prices, charges, and payment levels associated with individual technologies; b) concerns comparisons of resource requirements and outcomes (or benefits) of technologies for particular applications, such as cost effectiveness, cost utility, and cost benefit.
Macroeconomic impact:	The impact of new technologies on national health care costs, resource allocation among different health programs or among health and other sectors, and shifts in the site of care, such as from inpatient to outpatient settings. Other macroeconomic issues that pertain to health technologies include the effects of intellectual property policies (e.g., for patent protection), regulation, third-party payment, and other policy changes on technological innovation, investment, competitiveness, technology transfer, and employment.
Efficacy:	Experimental effectiveness; efficacy refers to the benefit of using a technology for a particular problem under ideal clinical conditions, e.g., within the protocol of a carefully managed randomized controlled trial, involving patients meeting narrowly defined criteria, or conducted at a "centre of excellence."
Effectiveness:	Effectiveness refers to the benefit of using a technology for a particular problem under general or routine conditions, e.g., by a physician in a community hospital for a variety of types of patients; thus, outcomes/effectiveness research emphasizes health problem-oriented assessments of care delivered in general or routine settings.

Comparative effectiveness:	Comparative evaluation of effectiveness
Efficiency:	cost and financial efficiency of a technology
Benefit:	Benefits – as positive impact –, but also costs, are conceptual categories that go beyond merely prices of goods and profits from investments, but include a variety of issues such as quality of life and efficiency of workflows.
Stakeholder perspective:	As the perspective of any evaluation is central to understanding the aim of the analysis, it is important gto make explicit as to whose perspective is taken in the analysis. Because the inter-connections of stakeholders in a health technology environment can be complex, it is important to define and record the stakeholder perspective taken in the evaluation.
Stakeholders:	In a healthcare setting, the five main stakeholder groups are (1) society, (2) citizens/patients, (3) healthcare professionals, (4) healthcare providers, and (5) third party payers.
Health outcome variables:	Used to measure the safety, efficacy, and effectiveness of health care technologies. Health outcomes have been measured primarily in terms of changes in mortality (death rate) or morbidity (disease rate). Of course, a wide variety of further measures are to be found in the literature.
Unit of outcome:	E.g. quality-adjusted life year (QALY).

The above mentioned 5 stakeholder groups can be characterised as follows:

(1) Society can be seen as a surrogate for the health system level and serves as a macro-level perspective for a given political system which has legislative power over health regulation and policy, be it a region, nation-state, or international organisation. This 'aggregate' stakeholder perspective is most useful for policy-makers/regulators to advise or inform technology-related policymaking.

(2) Citizens include also people who are not patients, but have an interest in services being available for their family now, or for themselves in the future – carers and patients.

(3) Healthcare staff includes various types of doctors, nurses, medical technicians, and administrative staff. Other categories can be added for staff whose working practices and arrangements are affected by the technology, but who are not users. These healthcare professionals and other workers can work in a wide variety of healthcare settings, including primary care and hospitals, and then in various roles, including emergency care, out of hours care, general and acute hospital care, and other services to citizens.

(4) Health services provider organisations can include General Practicioner (GP) practices, general hospitals, specialised hospitals, teaching and university hospitals, and social care organisations.

(5) Third parties includes health insurance companies and other payer bodies, as well as authorities or government organisation that could be affected without having the explicit role of reimbursing health care professionals HPOs for health services.

The perspective of the assessment, i.e. the stakeholders above, must not be confused with the ultimate recipient or sponsor of HTA, usually the policy-maker or a regulatory agency – as the goal of technology assessment is to provide policy-makers with information on policy alternatives.

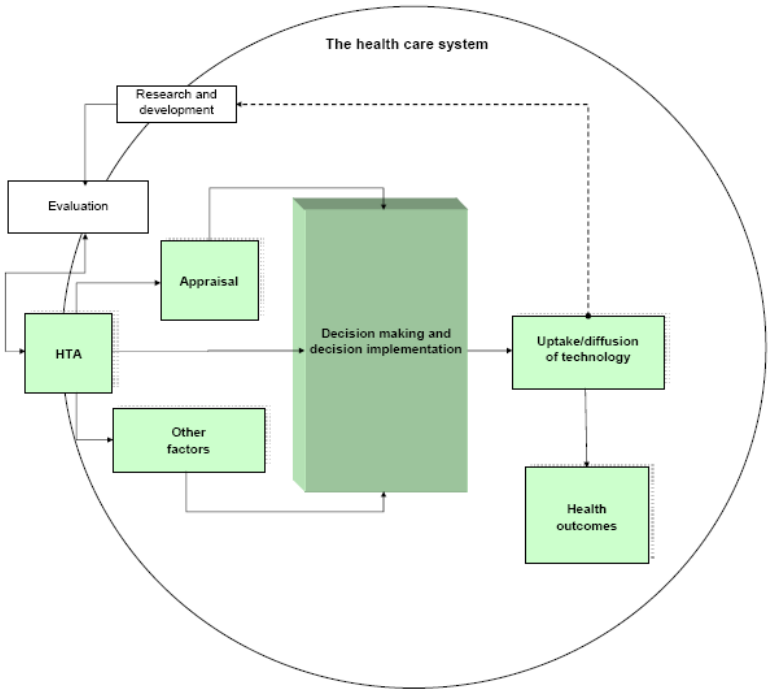
3.3. The health technology decision-making process

3.3.1. HTA and the health technology decision-making level

As was already mentioned earlier, HTA is primarily an instrument and approach to support rational decision making in healthcare systems on whether to invest in and implement improved or new medical technologies and devices. Therefore we will briefly explore the role of HTA in policy decision-making processes and implementation considerations. In few fields of public policy are the uses, benefits, but also the costs of services so powerfully driven by technological innovation as they are in health care,[4] and it seems that health technological innovation never ceases.

Figure 1 below links technology uptake and diffusion with research and technology developments that take place. This link is created by the various signals (including price and volume) sent from the healthcare system to the research and development community and its (industrial) suppliers.

Figure 1: Generic view of HTA and the health-care decision-making process



Source: OECD, Health technologies and decision making, 2005, p. 22.

[4] The Congress of the United States, Congressional Budget Office (CBO). Technological Change and the Growth of Health Care Spending. Washington, D.C.; 2008

Decision making in any health-care system is a complex set of interactions amongst a wide array of players. However, it is possible to categorise the different types of decisions made in different levels of the health-care system. In broad terms, decisions can be categorised into three levels:

- Macro (decisions made at national, provincial or Third Party Payer level).
- Meso (decisions made at regional health authority or hospital level).
- Micro (decisions made at provider or patient level).

As the levels of decision making can be categorised in this way, a technology should likewise be studied at macro level (such as national policy, wider social norms and expectations), meso level (such as organisational processes and routines), and micro level (such as particular experiences of patients and professionals), and both qualitatively and quantitatively to build a rich, contextualised picture of complex change.[5]

The rate of diffusion and the level of uptake of new health-care technologies are the aggregate outcomes of a large number of decisions made by politicians, health-care administrators, doctors and patients, but also health technology and medical device manufacturers. The political, organisational, and economic environments typically shape these decisions. HTA supports evidence-based planning and not a policy tool in itself. This means HTA should be regarded as an overarching determinant only on policy and practice, because of its aim to influence decision making through the application of high quality evidence and appraisal of that evidence.

3.3.2.Dimensions of decision support and regulation in healthcare policy-making

In order to contextualise the function of HTA as decision support in the regulatory environment of healthcare policy-making, the concrete instruments for translating policies into action help to understand the potential impact technology assessments can have. Before concluding this section on policy decision-making process and implementation with the limitations budget impacts pose for evaluating economic effects, the below Table 3 provides an overview of the dimensions that can be assigned to health policy and regulatory instruments.

TABLE 3: DIMENSIONS OF DECISION SUPPORT AND REGULATION IN HEALTHCARE POLICY-MAKING

Policy implementation level	Decision-making instrument/ Policy translation	
	Research and development	Healthcare delivery
EU and nation-state political system	Basic law and constitution (EU: treaties) National research policy Innovation policy Appraisal across innovation cycle, feedback into R&D	Basic law and constitution (EU: treaties) Social welfare policy

[5] See Greenhalgh, T., K. Stramer, et al. "Adoption and non-adoption of a shared electronic summary record in England: a mixed-method case study." BMJ 340: c3111.

National and regional health system	Legislative process Research budget measures Conditional approvals for funding/ reimbursement Develop policy documents	Legislative process (health policy and health system regulation) Budget measures Development of national clinical guidelines Approvals for funding/ reimbursement Recommendations and development of specific health programmes Disinvestment strategy Develop policy documents
Local level/ network of hospitals	Research project funding and grant making Appraisal across innovation cycle, feedback into R&D	Development of local clinical guidelines
Hospital	Research project funding and grant making	Development of hospital clinical guidelines
Patient-clinician		Liability, implementation of guidelines
Private health insurance level		Reimbursement and out-of-pocket

The following definitions are applied in this context:

Regulation: "Sustained and focused control exercised by a public agency over activities that are socially valued."[6] Regulatory activities, however, often point to a diffusion of regulatory capacities among a range of state, non-state, and supranational actors. Resources relevant to the exercise of power within regulatory regimes include legal authority, wealth, organisational capacity, information, and the capacity to bestow legitimacy.

Decision-making process: The decision-making process can be generally characterised by the observation that access to high-quality evidence is necessary but not sufficient to ensure rational uptake and diffusion of health technologies. The rational use of evidence depends, in large part, on the decision making process and on the institutional, organisational, political and cultural dynamics of health care systems. Decisions about the uptake and diffusion of health technologies take place at multiple levels of the health care system. Where clear decision-making structures exist, the impact of HTA evidence on decisions will likely improve, as HTA practitioners will be better able to direct their assessments to pre-defined target groups.

Policy decisions: The number of relevant regulations proposed, passed and enforced.

[6] Selznick, P. Focusing Organizational Research on Regulation. In: R. Noll (ed.). Regulatory Policy and the Social Sciences. Berkely: University of California Press, 1985

3.3.3.Economic evaluation and budget impact

When introducing a new health technology, the economic effects are of paramount importance to the healthcare system. Yet the assessment of budget impact has to be distinguished from economic evaluation.

While the latter depicts the relative economic value of two alternative technologies, a budget impact analysis addresses the *affordability* in predicting the impact of the introduction of a new technology on a particular budget holder's budget. It serves additional informational needs as decision makers in healthcare often have to operate within given budgets. Even if the cost-effectiveness of a technology is favourable, it can still be not affordable without overspending, and a reallocation of resources, however socially beneficial, is often politically difficult.

Budget impact analysis enables health policy makers to identify potential conflicts between a comprehensive societal assessment and an assessment from the perspective of a particular third party payer or health care provider and to recognize the need for additional intervention, research or testing. In order to ensure the successful diffusion and deployment of a new technology, e.g. healthcare financing arrangements can be changed or research grant making and policy can be re-adjusted or adapted accordingly.

Budget impact analysis also varies in methodology as it has to meet the needs of the targeted decision-maker which can differ from what is customarily provided in efficiency analysis. Instead of the societal perspective for example, decision-makers are rather interested in the relevant costs that will incur to their particular budget, as mostly they cannot profit from savings occurring in any other area. Similarly, the time horizon might be unapt as compensating overspending in the short term with savings occurring sometime in the future may be no feasible option. Besides the estimated market diffusion of a new technology and the impact its implementation has on service delivery, a budget impact analysis should address whether it has a substitution potential or would require additional funding, and imply what this means for the decision-maker, accounting not only for the acquisition cost but also for the financial consequences over time.[7]

[7] See Hartz, S. and J. John (2008). "Contribution of Economic Evaluation to Decision Making in Early Phases of Product Development: A Methodological and Empirical Review." International Journal of Technology Assessment in Health Care 24(4): 465-472.

4. VPH-focused framework

To progress towards an HTA approach which is amendable towards the specific requirements of the VPH modelling and computer aided medicine context, this chapter explores a life-cycle approach towards what has been called Technology Readiness Level (TRL), or, as we prefer it, the respective RTD workflow stage of the technology to be assessed, and identify specific verification and validation approaches compatible to the respective stage reached. Next, decision-related impact and assessment levels are briefly explored, followed by a discussion of the temporal dimension of assessments.

4.1. RTD workflow stage & assessment approaches

As discussed earlier, standard HTA concerns itself usually with - more or less - proven technology to be introduced across the healthcare system, or to be applied in a modified/different context, and compares it with already matured and widely diffused ones.

For our purposes, in a swiftly changing technology environment, and to improve upon present decision making, this is not sufficient. To expand on this dimension, we consider in HTA the complete life cycle of a new or modified technology, ranging across all development stages, which are also named Technology Readiness Level (TRL).

Technology Readiness Level (TRL) is a measure used by some United States government agencies and also large private businesses to assess and classify the maturity of high-risk and evolving technologies (materials, components, devices, etc.) prior to incorporating that technology into a system or subsystem.[8] Generally speaking, when a new technology is first invented or conceptualized, it is naturally not suitable for immediate application or deployment. Instead, new technologies are usually subjected to experimentation, refinement, and increasingly realistic testing, which, in the case of VPH technologies, refers to clinical testing. Once the technology is sufficiently proven, it can be incorporated into a system/subsystem.[9]

For the purpose of MD-Paedigree technology assessment, introducing the concept of technology readiness levels provides a comprehensible overview of the technologies' maturity at any given time. It is thus an innovative, cross-disciplinary approach and follows a formative assessment approach, which is needed to address the dynamic aspects of evolving VPH technologies. Furthermore, to underline the continuous, usually also recursive and iterative nature of RTD processes, we prefer to talk about RTD workflow stages rather than the more static connotation of "readiness" levels.

Concerning the VPH technology RTD workflow stages, we propose the following 11 distinct stages as outlined in Table 4 below. As will follow immediately from the descriptions of these stages, the, assessment approach applied at each stage must be appropriate for the respective RTD workflow stage, and it must be able to reflect the specific evidence needed for rational decision taking on modification of results achieved and/or whether to progress to the next stage.

[8] US Department of Defense (2006): Technology Readiness Levels in the European Space Agency (ESA) and the US Department of Defense. In: Defense Acquisition Guidebook. Online: http://akss.dau.mil/DAG/

[9] United States General Accounting Office: (1999): Better Management of Technology Development Can Improve Weapon System Outcomes. Online: http://www.gao.gov/archive/1999/ns99162.pdf

TABLE 4: VPH TECHNOLOGY RTD WORKFLOW STAGES AND CONCOMITANT ASSESSMENT METHODS

RTD workflow stage	Description	Testing & assessment approach
1	Idea exploration, identification of basic principles	***Proof-of-concept**/feasibility demonstration*
2	Formulation of concept, hypotheses and/or application	
3	Defining analytical & experimental critical characteristics and functions, proto-model programming	
4	Design and construction of tool/model/application	*Experimental **verification** and preliminary **validation***
5	Parameterisation and configuration	
6	Testing of principal functionalities in laboratory environment	
7	Prototype feasibility demonstration (clinical or laboratory observation)	*Pre-clinical validation & ex ante **efficacy** assessment*
8	tool/model/application safety testing in clinical environment	*Pre-clinical & clinical **trials** (validation & **effectiveness**); efficiency/ **benefit-cost** assessment*
9	Comprehensive testing of tool/model/application and approval	
10	Implementation for routine use in clinical environment	***Business planning***
11	Diffusion, improvements	*Postmarketing & user **feedback***

4.2. Impact and assessment level

As mentioned earlier, any HTA will serve a distinct purpose, which usually is decision support in the context of a specific health policy issue. If we accept that HTA is concerned with the above identified development or RTD workflow stages, we need to clarify at which impact (or policy issue) level the specific HTA under consideration may be applied. We propose to differentiate these assessment levels as follows:

a) Technology itself, with two subclasses
   - simple technology (e.g. a [partial] simulation model)
   - complex technology (e.g. multi-scale or hypermodel)

b) Health
   - individual person
   - groups of persons/populations

c) Health system/society

Whether only one or several of these impact levels will be considered in any specific HTA will have to depend on the context and objectives pursued. When implemented, HTA based decisions, however, will always influence health impact and health outcome through health practice, i.e. through the health system.

4.3. Temporal dimension and level of comparison

Considering the time dimension, two basic distinctions can be applied:

a) Static

In a static context, usually two technologies are compared as given at that point in time. Note that this need not imply a comparison at a unique instant in time; a thorough assessment may require to observe and assess the impact of both technologies for a given period, like in an RCT (randomised controlled trial).

b) Dynamic

In a dynamic environment, we may distinguish as follows: one may want to assess the likely development path of a technology at an early stage of research or development and attempt to forecast/assess its likely impact in the future as it becomes more mature and may be implemented and diffused. This may be compared with

- the presently observed impact of an established, mature technology which is expected no longer to change in the course of time, or
- with the expected future impact of a competing technology which may also be developed further over time.

Note that in a dynamic context, dependent on the development stage of the technology, certain impacts may already undergo concrete assessment like the accuracy of a model, but its future health impact may only be forecast at a very rough level of precision.

Another important consideration under this dimension is whether the

a) short-term

b) medium-term, or

c) long-term

impact is assessed. E.g., diuretics applied to treat heart failure have a quite considerable short-term beneficial impact, but have turned out to be quite often rather detrimental in the longer term.

Furthermore, in a dynamic context as will be usual for the further development and implementation of VPH-based technologies, it will be important to estimate and assess the likely

- further path of learning of the system implemented, like its increasing accuracy of predictions of likely disease progression for a particular patient as more data from past experience emerge, the impact of treatment options and the like,
- the rate and shape of the diffusion curve over time
- the temporal end point of the saturation level across healthcare provider organisations.

These are aspects of core relevance when estimating the likely long-term impact of VPH technologies – aspects which are neglected in conventional HTA assessments.

5. Measuring benefits and costs

This chapter starts with a brief presentation of benefit-cost analysis and a discussion of some core concepts and challenges when considering to measure benefits and costs of a health technology such as VPH models. It then explores some concrete measures and tools to indeed identify and measure such benefits and costs.

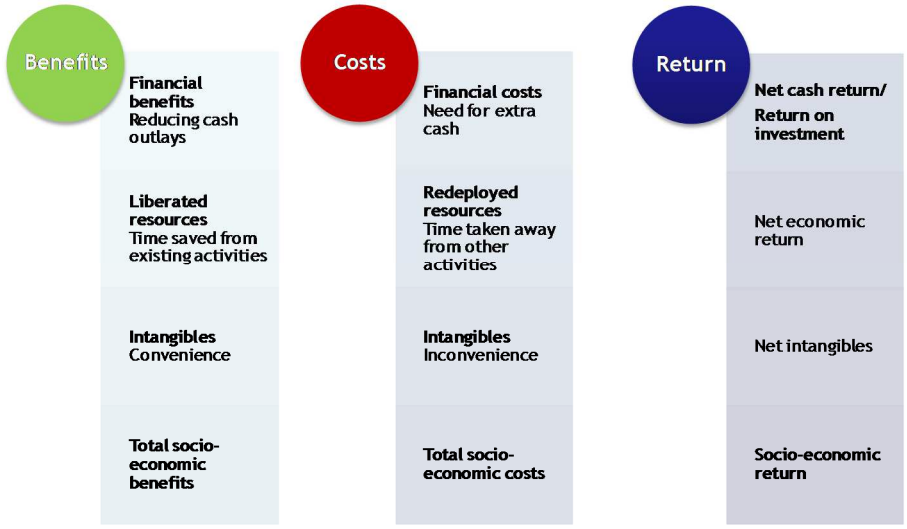
5.1. Benefit-cost analysis

The UK Treasury 'Green Book'[10] provides a useful definition of cost-benefit analysis (CBA) as

> *"Analysis which quantifies in monetary terms as many of the costs and benefits of a proposal as feasible, including items for which the market does not provide a satisfactory measure of economic value."*

CBA aims to determine whether, and to what extent, a planned (ex-ante) or completed (ex-post) project or programme has been worthwhile. The CBA's aim of reflecting reality in practice means to define a unit of analysis and separate it into distinguishable impacts (see Figure 2). These impacts can be observed when they show a positive or negative effect on a stakeholder. Impacts are operationalised through a set of associated techniques.

FIGURE 2 - TYPES OF COSTS, BENEFITS, AND RETURNS



Applying clinical use cases and concrete application scenarios as detailed descriptions of potential futures allows for the identification of core

- health system actors,
- technologies,
- work flows and steps,
- any other factor or variable

[10] HM Treasury, 'The Green Book on Appraisal and Evaluation in Central Government', 2003

impacting on or being impacted by benefits and costs to be recorded or estimated. To realise this, it will be necessary to develop a realistic process model of the currently implemented pathway(s) and measure (or estimate) the related outcomes/benefits as well as inputs and their costs.

This needs to be contrasted with a newly developed process model reflecting the envisaged implementation of the deployable MD-Paedigree technology components, and then estimating their potential benefits as well ad implementation and service costs. This new pathway (model) must be aligned with the foreseeable optimal use of MD Paedigree technologies, databases and instruments.

5.2. Operationalisation of measures

5.2.1. Simple and complex measures

Positive impacts are sometimes easy, and sometimes very difficult to measure. Depending on the RTD workflow stage of the technology under scrutiny, key operationalisations may relate to the verification and validation of the simulation models like the capability or accuracy of models – which is not our concern here, and at later stages e.g. improved health outcomes for individual patients or populations, costs saved for the health system, reduction of hospital admissions, avoidance of medications to take, or also monetarised benefits like waiting time or travel time and costs saved.

The same applies to negative impacts, which may be higher financial costs, more complex interventions, inconvenience to users, loss of hierarchical power due to new clinical pathways, time lost, etc.

Complex *measures* (or also sometimes termed *indicators*) establish a specific relationship between single measures, like quality of life years (QALYs). It is a measure of disease burden, including both the quality and the quantity of life lived. This measure is, e.g., often used in cost-utility analysis to calculate the ratio of cost to QALYs saved for a particular health care intervention.[11] This is then used to allocate healthcare resources, with an intervention with a lower cost to QALY saved (incremental cost effectiveness) ratio ("ICER") being preferred over an intervention with a higher ratio.

Another example is efficiency, which in its generic form is an empty concept of an output/input relationship. Principal efficiency concepts concern economic/financial and technical efficiency measures, others may concern energy or pollution. Concerning e.g. health outcomes, a certain technology is deemed to be more cost efficient than another if it either achieves the same health outcome with a less costly (in monetary terms) input (or a better outcome with the same input costs), or if it achieves a comparatively higher health outcomes with relatively little higher costs. A benefit/cost analysis compares the ratio of the monetised positive impacts (benefits) to the monetised negative impacts (costs), and the technology with the higher ratio is the one to be preferred.

5.2.2. Context dependency of measures

It must be noted that all impact measures are not neutral but rather context dependent. What is e.g. a benefit to one stakeholder (like income) may be a cost to another. Or what is regarded by one person as a highly negative impact (like a shorter life from smoking) may be regarded by another one as a negligible negative impact compared to the pleasure derived from smoking.

Another aspect is that a decision towards, e.g., an option with a higher benefit/cost ratio may not be feasible due to affordability constrains, i.e. the financial means to secure the inputs needed to achieve the desired result may not become available to the stakeholder.

[11] http://en.wikipedia.org/wiki/Quality-adjusted_life_year

5.2.3.Assessment processes, methodological approaches to measurement

Another highly disputed issue is the preferred assessment methodology to be used. There is no consensus opinion in the literature on, e.g., whether also for HTA RCTs would be the gold standard. Other constraining factors are the time span, human and financial resources available to per-form an HTA. On these aspects further discussions have to be followed up upon in this section at a later stage.

5.3. Benefits

Conventional HTA is usually restricted to look at a given point in time (or short period) at just a single, newly intervening variable, and then measure the benefits and costs related to it – compared to the "old" or standard comparator technology respectively intervention. Quite often this involves estimating the benefits for "the patient", for the healthcare system as such, or for society at large only.

In more complex change situations such as introducing a new VPH-based decision support system or a computer aided medicine intervention, such an approach is not sufficient to assess the eventual success perspective. As discussed above, there are two critical dimensions towards estimating future benefits:

- The temporal or RTD workflow stage as outlined above must be taken into account,

which requires both evaluation approaches adjusted to the respective stage achieved and a dynamic perspective covering several years; aspects discussed elsewhere in this report.

A similarly critical aspect is that such new interventions as developed by VPH projects like MD Paedigree tend to not change just a single variable but rather lead to more fundamental changes like a quite different clinical pathway, which needs to be compared to the standard diagnostic and/or treatment path prevailing so far. This implies looking at a multitude of variables which leads to much more complex methodological issues as discussed in this report. A core aspect is that such a change usually will impact various stakeholder groups, from which it follows that

- All stakeholders involved must have a business case,

i.e. we need to examine whether and how a 3W - win-win-win - situation can be achieved such that all relevant stakeholders are onboard and support – or at least will not block – the introduction and diffusion of the new technology. This concerns particularly

- ✓ Patients
- ✓ Medical professionals
- ✓ Healthcare provider organisations (hospitals, community centres, ...)
- ✓ Third Party Payers
- ✓ (Health), local/regional politicians

Tangible benefits to be considered, operationalised and measured involve items like

- Higher income/turnover (from more or new patients)
- Improved reimbursement/charging of newly introduced DRGs (diagnosis-related groups)
- Direct costs saved (like for bed capacity, travel, lab examinations, drugs avoided, ...)

Intangible benefits include

- Improved patient safety (like fewer serious drug interactions recorded)
- Improved outcomes (death, disease, days in hospital or in rehabilitation, QoL score, QALYs, ...)
- Convenience (higher work satisfaction, more professional contacts, faster learning)

- Competitive position (more patients served; more privately paying patients among the clients; extension of catchment region)
- Staff satisfaction (fewer complaints, easier agreement to substitute or exchange work time, staff retention rate improved, ...)

Measurement tools and data gathering approaches include reading data from paper and electronic records such as accounting systems, reports, management information systems. Others involve data gathering and obtaining estimates from administration, clinicians, staff, other experts, other stakeholders. On clinical data, medicine literature very often provides for detailed and well researched data. Interviews or even focus group discussions may become also useful procedures.

Estimating the monetary value of intangible impacts may involve further data gathering techniques. Revealed preference can be used to estimate time savings of professionals. An average salary is used as a proxy to attach a monetary value to it. For the valuation of others a stated preference approach can be used. Willingness to pay or willingness to accept are further options.

5.4. Costs

The cost model applied in a concrete assessment situation should be based not on a singular intervention or factor, but rather based on a comprehensive use case presenting the present standard of care respectively the (future) new patient pathway. Such a clinical use case will then reflect and gather data on the total cost of ownership for this instance.

Cost items to be considered concern

- Investment expenditure/depreciation costs
- Labour (wages, fringe benefits, etc.)
- Instrumentation/medical device and other operating/maintenance costs
- General overhead.

Wherever possible, costs should be based on real costs; however, quite often healthcare provider organisations and other health system actors do not avail themselves of professional cost accounting systems. Then professional or expert estimates and other data gathering methods as outlined earlier will need to be applied.

Tables 5 and 6 below present initial simple schema to collect basic cost data for a present standard of care pathway respectively a future care pathway supported and facilitated by VPH/MD-Paedigree technology.

TABLE 5: SCHEMA TO COLLECT BASIC COST DATA FOR PRESENT STANDARD OF CARE PATHWAY

	Pathway Step	Clinical Use Case	Service Use Case	Deployable Component / Unit	Instrumentation		Labour costs			Comments and sources	Sums [€]	Patient Distribution / Pathway)
					Cost per Unit [€]	Purchase price [€]	Labour costs per Unit [€]	Time per Unit	Labour Cost [€]			
Standard of Care	Visit											
Max Cost Pathway [€] (Total sum)												
Cost per Cohort [€]												

Table 6: Schema to collect basic cost data for VPH-supported care pathway

	Pathway Step	Clinical Use Case	VPHOP Service Use Case	Deployable Component / Unit	Instrumentation		Labour costs			Comments and sources	Sums [€]	Patient Distribution (/ Pathway)
					Cost per Unit [€]	Purchase price [€]	Labour costs per Unit [€]	Time per Unit	Labour Cost [€]			
New												
	Cost per patient											
	Cost per subset of cohort (100 - L)											

6. Methodology of generic impact scenario approaches

The final goal of the planned impact assessment is to develop and estimate a high-level generic benefit-cost scenario for exploring the potential clinical (and socio-economic) impact of MD-Paedigree applications.

6.1. Review of scenario approaches

A scenario can be defined as "an internally consistent view of what the future might turn out to be – not a forecast, but a possible future outcome."[12] The point about scenarios is they give a consistent elaboration (extrapolation) of a certain theme expected to play an important role in the future. In this sense they are akin to Weber's 'ideal type' descriptions: not intended to be a description of the empirical phenomena, but an exaggeration to highlight an important principle or dimension. On this basis, the emphasis in Porter's definition of a scenario should be on 'possible future outcome', for it must be empirically possible, but does not have to be probable (as a forecast intends to be).[13]

In a world of increasing complexity, scenarios are a strategic tool to help prepare for possible futures.[14] In other words, scenario planning or scenario thinking has been defined as a strategic planning method that is used to make flexible long-term plans.[15] Scenario planning can also be described as a method for learning about the future by understanding the nature and impact of key uncertain, but important driving forces affecting our future[16]. Consequently, it depends on information about social, technological, economic, ecologic, politics and values related developments, referred to under the acronym STEEPV.[17] A slightly different classification outlines political, economical, social/cultural, technological, ecological and demographical trends (PESTED) to be taken into account. In line with the objectives stated earlier, the focus of our analysis will be on clinical, economic, social/cultural and organisational/transformational aspects and impacts, together with also considering interdependencies with technological developments and the policy framework.

A further differentiation made by some authors includes scenario building and scenario planning.[18] Building scenarios means speculating about the uncertainty surrounding the future: basically it means envisaging a few different possible future outcomes for the situation under scrutiny or, in the word of the Swedish neurobiologist David Ingvar, to create "memories of the future."[19] In this understanding, scenario building is the necessary foundation for scenario planning, a management technology used by managers to articulate their mental models about the future and thereby make better decisions.[20] Others link scenarios with planning. Wilkinson elucidates how scenario planning can prepare us in the same way that it prepares corporate executives: it helps us understand the uncertainties that lie before us, and what they might mean. It helps us 'rehearse' our response to those possible futures. And it "helps us spot them as they begin to unfold."[21] Scenario planning can be regarded as a tool for improving decision-making against a background of possible future environments. It is an internally consistent account of how the business environment and

[12] Porter, M.E. (1985). Competitive advantage : creating and sustaining superior performance. New York, Free Press
[13] Enders, J., et al., Eds. (2005). The European Higher Education and Research Landscape 2020 : Scenarios and Strategic Debates. Enschede, University of Twente, CHEPS
[14] Tielens, T., KNCV scenarios: chemistry in 2030, in APC Conference2003: Delft
[15] http://en.wikipedia.org/wiki/Scenario_planning
[16] Scenario planning resources http://www.well.com/~mb/scenario/#What_is_Scenario_Planning
[17] Loveridge, D., *Foresight and Delphi processes as information sources for scenario planning, ideas in progress*, 1999, PREST: Manchester.
[18] Mietzner, D. and R. Guido, *Scenario-Approaches–History, Differences, Advantages and Disadvantages*, in *EU-US Scientific Seminar. New Technology Foresight, Forecasting & Assessment*2004: Seville, Spain
[19] Schwartz, P. (1998). The art of the long view : planning for the future in an uncertain world. Chichester, Wiley
[20] Georgantzas, N.C. and W. Acar (1995). Scenario-driven planning : learning to manage strategic uncertainty. Westport, Conn ; London, Quorum Books
[21] Wilkinson, L. (1996). "Scenarios: Special Wired Edition." Wired Magazine.

external environment in which an organization operates might develop over time. There is also an understanding that an organisation might build up a range of scenarios over time to make sense of diverse but interconnected factors in the external environment and to deal with critical uncertainties."[22] Scenarios create a process that is conducted by analysis and shared understanding of contextual factor analysis.[23] A basic principle of scenario planning is that it involves a learning process based on cooperation and disagreement between individuals, leading to co-producing and internalizing a shared meaning and understanding, as well as articulation of potential differences in opinion.[24] If done properly, the process tends to force the collaborative analysis to redefine or reframe political arguments based on shared understanding of contextual information.[25]

Content wise, scenarios can be analysed along different dimensions that allow situating an exercise in the diversity of exercises. The main qualitative concerns are summarised in the table below:

TABLE 5: MAIN DIMENSIONS RELATED TO SCENARIO CONTENT

Scale(s)	Global, supranational, national, sub-national, regional and local, vertical integration
Main focus	global & integrated, area-based, issue-based, institution-based, etc.
Time horizon	Short, medium, long term
Temporal nature	Snapshot or chain scenario
Variables	Qualitative/quantitative, etc.
***Dynamics* (within one scenario)**	Trend or peripheral
***Level of deviation* (between the scenarios of the exercise)**	Alternative (high)/conventional (low)
***Diversity of perspectives* (in one scenario)**	Yes or no
Inclusion of norms?	Yes or no/ implicit vs explicit
Level of integration	High or low

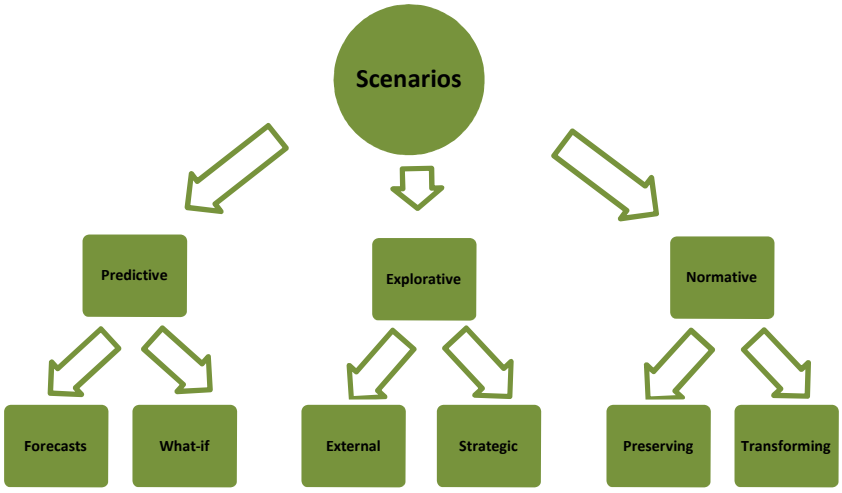
Source: Goeminne, Jempa and Mutombo[26]

6.1.1.Scenario categories

Literature on the subject commonly denotes three modes of thinking associated with different types of scenarios.[27]

FIGURE 3: SCENARIO TYPOLOGY BASED ON THREE BASIC MODES OF FUTURE THINKING

[22] ETTE (2002): Focus in the Future of Vocational Education and Training, Melbourne, 2002, p. 12
[23] Schoemaker, P. (1993). "Multiple scenario development: Its conceptual and behavioural foundation." *Strategic Management Journal* 14(3): 193-213.
[24] Ramirez, R., J.W. Selsky, and K. Van der Heijden, Eds. (2008). Business planning for turbulent times : new methods for applying scenarios. London, Earthscan
[25] rvidsson, N. (2010). Designing more effective political governance of turblulent fields: The case of healthcare. *Business planning for turbulent times : new methods for applying scenarios*. R. Ramirez, J.W. Selsky, and K. Van der Heijden. London, Earthscan
[26] Goeminne, G., E. Jempa, and K. Mutombo (2007). "The Field of Scenarios: fuzziness as a chance for building appealing future visions." Working paper for the CONSENTSUS project.
[27] See Amara, R. (1991). "Views on futures research methodology." Futures 23(6): 645-649. Dreborg, K.H., Scenarios and structural uncertainty: Explorations in the field of sustainable transport, 2004, Department of Infrastructure, Royal Institute of Technology: Stockholm. Börjeson, L., et al. (2006). "Scenario types and techniques: Towards a user's guide." Futures 38(7): 723-739.



Source: Börjeson et all.[28]

6.1.2.Predictive Scenarios

Predictive scenarios are commonly differentiated according to the conditions they impose on what will happen. Forecasts respond to the question: what will happen, on the condition that the likely development unfolds? What-if scenarios respond to the question: what will happen, on the condition of some specified events?

Forecasts, responding to the question "what will happen, on the condition that the likely development unfolds, are conditioned by what will happen if the most likely development unfolds, i.e. when making a forecast the basic supposition is that the resulting scenario is the most likely development. Forecasts can be used as an aid for planning in, for example, the business environment. In such cases, forecasts are made of external factors[29] such as economic events, natural phenomena and organisational statistics. Those forecasts are most suited to the short term, when the uncertainty in the development of the external factors is not too great.[30]

What-if scenarios, responding to "what will happen, on the condition of some specified events?", investigate what will happen on the condition of some specified near future events of great importance for future development. The specific events can be attributed external events, internal decisions or both. What-if scenarios can consist of a group of forecasts, where the difference between the forecasts represents a 'bifurcation' and where the specified event acts as the bifurcation point. None of the scenarios is necessarily considered as the most likely development. As a consequence, the resulting what-if scenarios reflect what will happen, provided one or more events happens.

6.1.3.Explorative Scenarios

Explorative scenarios are characterised by the openness to several possible future developments and encompass an external and strategic mode.

External scenarios focus on external factors beyond the control of the relevant actors. They are typically used to inform strategy development of a planning entity and provide a framework for the development and assessment of policies and strategies. The external scenarios can then help the user to develop robust

[28] Börjeson, L., et al. (2006). "Scenario types and techniques: Towards a user's guide." *Futures* 38(7): 723-739.
[29] External factors are those that are not controllable by the actor or scenario user in question, contrary to internal factors such as policy measures which are at the hand of the intended scenario user to cope with the issues at stake.
[30] Ibidem

strategies, i.e. strategies that will survive several kinds of external development. In the case of certain global climate scenarios, for example, the outcome depends on assumptions regarding how the atmosphere and the sea absorb climate gases. Different developments are possible depending on how those ecosystems react and therefore the resulting scenarios then form a basis for discussions on different measures. In a business context, external scenarios can be used for companies and organisations, whose influence on external factors is obviously small, to find flexible and adaptive solutions. External scenarios may also make the organisation more receptive to weak signals of radical changes in the actor's environment.

Strategic scenarios, responding to the question "what can happen if we act in a certain way?", integrate internal factors, i.e. (policy) measures at the hand of the intended scenario user to cope with the issue at stake. The aim of strategic scenarios is to describe a range of possible consequences of strategic decisions. While external factors are taken into account, the main focus is on internal factors (i.e. factors that can possibly be affected). Strategic scenarios describe how the consequences of a decision can vary depending on which future development unfolds. Different policy approaches are typically tested and their impact on target variables are defined.[31]

6.1.4.Normative Scenarios

Normative scenarios usually respond to "how can the target be reached?" and are based on a mode of thinking that envisages how society or some sector or activity could be designed in a better way than its present mode of functioning. This mode of thinking suggests solutions to fundamental societal problems by taking normative goals into account and exploring the paths leading to these goals.

Transforming scenarios are elaborated when a marginal adjustment of current development is not sufficient, and a trend break is necessary to reach the target. The backcasting method is mainly used (see the next paragraph on methodologies) and typically results in a number of target-fulfilling images of the future, which present a solution to a societal problem, together with a discussion of what changes would be needed in order to reach the images. It has a rather long time-perspective of 25–50 years.[32]

Preserving scenarios are developed to find out how a certain target can be efficiently met by adjustments to the current situation. Here, it is assumed that the target can be reached within a prevailing structure. Targets can concern environmental, social, economic, technological as well as cultural factors, typical examples being cost or eco-efficiency. Optimising the set of technology and policy measures in order to meet a certain greenhouse gas emission level is an example of a preserving scenario type as has been done in the IPCC (Intergovernmental Panel on Climate Change) scenarios.

6.1.5.Aspects, dimensions and approach for scenarios of healthcare delivery

Given the *extreme complexity* of (national) health systems, the number of actors involved in even relatively simple healthcare delivery processes, the political sensitivity of any health-related policy issues, and the mix of powerful stakeholder groups lobbying in this field, scenario planning should indeed be preferred to other more formalised methods of analysis. Scenarios thus permit a rethinking of the structure and boundaries of healthcare systems, as well as the nature and role of these stakeholders in the pursuit of sustainable health systems.[33]

Considering the task given for this work, developing exploratory scenarios is asked for, and the following four observations relating to such scenarios are particularly relevant:

[31] Ibidem
[32] Robinson, J.B. (1990). "Futures under glass: A recipe for people who hate to predict." *Futures* 22(8): 820-842
[33] World Economic Forum (2013). Sustainable Health Systems - Visions, Strategies, Critical Uncertainties and Scenarios

- The future is not only a continuation of past relationships and dynamics but can also be shaped by human choice and action.
- The future cannot be foreseen, however, exploration of the future can inform the decisions of the present.
- There is not one possible future only, uncertainty calls for a variety of futures mapping a 'possibility space'.
- The development of scenarios involves both rational analysis and subjective judgement; it therefore requires interactive and participative methods.[34]

6.2. Scenario method to be applied

A widely reported methodology in the context of explorative scenarios, comprising five main steps, is the one described by Peter Schwartz, firstly in the book The Art of the Long View,[35] and later on, e.g. with Jay Ogilvy for the Global Business Network (GBN)[36]. The five steps are the following:

1. Decision focus: Identify the focal issue or decision: What are the central concerns and key issues of the users of the scenarios?

2. Key factors: Identify the driving forces that are likely to have the most important influences on these central concerns of the future.

3. Pre-determined elements and uncertainties: Which of these driving forces seem pre-determined and inevitable and which are the factors which seems likely to change the direction of the scenarios?

4. Selecting the scenario logics (or scenario plots): Ranking of the drivers by their importance and their uncertainty and identifying two or three critical factors of the central themes of the scenarios.

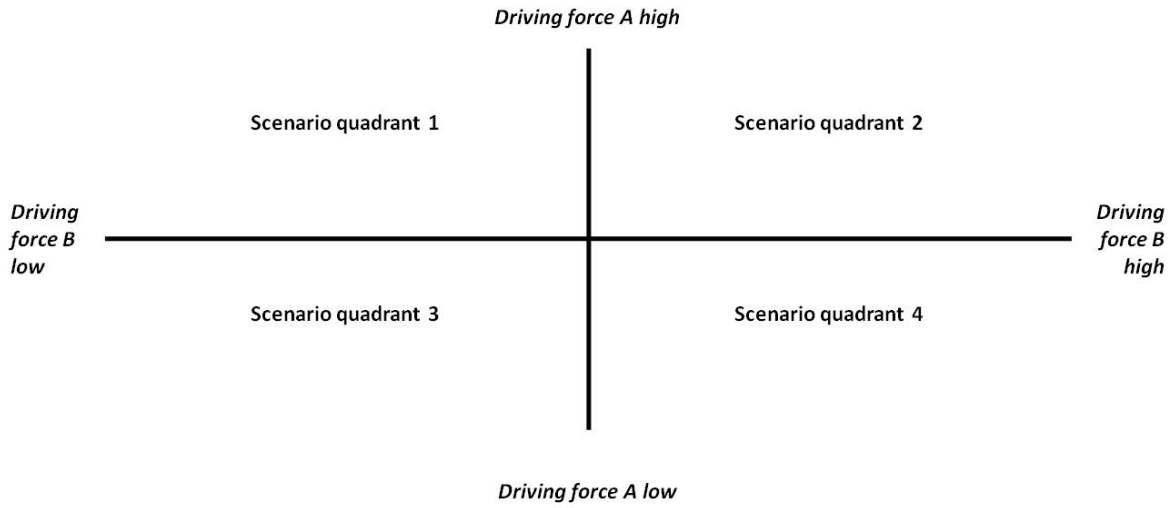
5. Fleshing out. Elaborating the basic scenario logics into full-fledged scenarios. This is often done in the form of narratives that present a plausible sequence of events.

   This final phase commonly includes modelling techniques that serve as a predictive tool (predictive mode) or as a tool to check the consistency and coherence of a scenario plot (explorative and normative mode). Quantitative data can be processed to illustrate the final scenario.

Building scenarios is usually a highly complex process requiring a comprehensive understanding of the issues at hand. Two somewhat different approaches can be identified in selecting the most relevant variables; one method can be described as *inductive*, the other *deductive.* The inductive method is less structured and relies on consensus building whereas the deductive approach or axes technique uses prioritization techniques to select the two most critical uncertainties. The widely-used four-quadrant scenario method is usually based on weighing the potential outcomes of a pair of uncertainties. Using a four-quadrant diagram (see Fig. 3) with the two uncertainty dimensions gives us four distinct *"what if"* scenarios in order to analyze different possibilities and present a range of potential scenarios in a logical, clear way.

FIGURE 4: SCENARIO AXES AS A STARTING POINT FOR SCENARIOS

[34] Mietzner, D. and R. Guido, *Scenario-Approaches–History, Differences, Advantages and Disadvantages*, in *EU-US Scientific Seminar. New Technology Foresight, Forecasting & Assessment*2004: Seville, Spain
[35] Schwartz, P. (1991). The art of the long view. New York, Doubleday/Currency
[36] http://www.gbn.com/articles/pdfs/gbn_Plotting%20Scenarios%20new.pdf


Driving force A high
Scenario quadrant 1
Scenario quadrant 2
Driving force B low
Driving force B high
Scenario quadrant 3
Scenario quadrant 4
Driving force A low

7. Generic VPH Scenario Planning approach

Following on from the discussion above on scenario approaches in general, in the specific context of the VPH so-called explorative scenarios are proposed to be applied for the MD-Paedigree context. These reflect both the specific purpose of this exercise and the speculative, uncertain nature of the overall scenario situation.

7.1. Introduction

In this chapter, we present the key steps towards developing such scenarios in a generic VPH context as well as outlining core variables and considerations to be applied to deliver the results required.

Initially we explore and identify central concerns and key issues of potential users of the scenarios to be developed; these users come from the health policy community and from those individuals developing and supporting eInfrastructures to allow our health systems to better meet urgent challenges. Next, those driving forces that are likely to have the most important influence on these central concerns of the future are discussed. From this a generic scenario plot is derived identifying the two critical factors of the central themes of the scenarios deemed most relevant.

This will be complemented with a brief exploration of key aspects of a socio-economic impact assessment, with a particular focus on clinical impacts. All of this will be reflected in elaborating the basic scenario logic into full-fledged scenarios in Chapter 6.

7.2. Key health system challenges

In almost any discussion of the focal issues and central concerns of today's health systems certain topics are repeatedly mentioned. As a first step, we identify these, reflecting both key policy challenges of European health systems and the opportunities offered by ICT-based new solutions and models like those under development by tMD-Paedigree.

Some of the most significant drivers and trends in healthcare have been identified as:[37]

- Demographic and social change (ageing of society and workforce; increasing life expectancy; changing family forms)
- Old and new disease threats (chronic diseases; environmental pollution; antibiotic resistance; modern living/lifestyle diseases: depression, obesity, drug addiction)
- Rising health awareness and so-called consumerism
- Individualised/personalised medicine
- Growing ubiquity of health informatics and telemedicine
- Understanding and exploitation of genomics, proteomics and other biomolecular sciences
- Other new medical technologies, and the resulting
- Increasing costs of health and social care provision.

[37] World Economic Forum (2013). Sustainable Health Systems - Visions, Strategies, Critical Uncertainties and Scenarios

7.3. Central factors and driving forces

7.3.1. Longer term challenges

Many of these challenges to the further advancement and long-term sustainability of our health systems such as the ageing process or certain diseases related to ageing like dementia and certain neoplasms, seem pre-determined and inevitable, and therefore difficult, if not impossible, to influence. Others factors can be influenced by bold policy-maker and stakeholder actions, and it is possible to identify two major domains where it seems likely for them to be able to change the direction of where healthcare is moving to in the longer term, if there is a will and if the resources needed to implement the necessary actions can be mustered.

7.3.2. Moving towards more integrated service provision

In many regional and national systems, particularly those of a Bismarck-type, the different types and levels of healthcare services are delivered independently or only loosely connected in a linear fashion, rather than as an integrated holistic service. Family doctors/GPs, specialists, secondary and tertiary hospitals, rehabilitation institutions and others operate as independent actors, not as integrated, coordinated teams cooperating towards seamless healthcare delivery. This often leads to inefficiencies, duplication of resources or reduced levels of quality of care.[38] Consequently, at the higher health policy level, moving towards more integrated service provision is seen as a key enabling factor to allow our health systems to better meet and cope with these challenges.

Here integrated service delivery is defined as "The management and delivery of health services so that clients receive a continuum of preventive and curative services, according to their needs over time and across different levels of the health system."[39] It is assumed that economic, political and socio-demographic forces will move the future healthcare system beyond the largely reactive acute care paradigm to a more holistic paradigm emphasizing optimization of the population's health [20]. At the core of this shift will be the movement away from episodic treatment of acute illness events to the provision of a coordinated continuum of services that will support those with chronic conditions and enhance the health status of defined populations.[40]

7.3.3. Investing in VPH RTD and clinical implementation

Achieving change in a system with limited resources will require a focus on future on cost-saving and productivity-increasing medico-technical applications and tools; this is becoming another grand challenge for the sustainability of our health systems. Whereas "roughly half of the increase in health care spending during the past several decades was associated with the expanded capabilities of medicine brought about by technological advances,"[41] we can expect that now finally the facilitating and enabling capacities of advanced information and communications technology systems and applications indeed will allow us to respond to these healthcare requirements favourably.

It is here were we can expect that VPH tools and services will, in the longer run, contribute fundamentally to and put medical progress into clinical context to improve prevention, diagnosis, and prediction of the likely impact of a given intervention, thereby helping to reduce treatment costs, not to further enlarge them, and

[38] The Congress of the United States, *Technological Change and the Growth of Health Care Spending*, C.B.O. (CBO), Editor 2008: Washington D.C.
[39] http://www.who.int/healthsystems/service_delivery_techbrief1.pdf
[40] Shortell SM, K.A. (2006). Health care management: organisation design and behavior. New York, Thomson Delmar Learning. Epping-Jordan, J.E., et al. (2004). "Improving the quality of health care for chronic conditions." Qual Saf Health Care 13(4): 299-305.
[41] The Congress of the United States, op. cited

at the same time improve service quality and patient quality of life. This would also involve a paradiagm shift away from transactional advantage – attempting to lower immediate costs – to transformational advantage – such that a fundamentally improved healthcare system will provide better outcomes for all at lower costs.

It is well known that such ICT services are in need of a sophisticated regional or even national infrastructure, eventually also a European-wide interoperability schema.[42] As such eInfrastructures are characterised by being able to generate huge benefits from externalities and spill-over effects, also known as network effects. Benefits which cannot be reaped by individual investors should be provided for by governments or larger groups of, e.g., public Third Party Payers as a public good to meet market failure in this field.

7.4. Selecting the scenario plots

Based on this analysis of the central challenges and key issues that confront our health systems, we identified a number of driving forces that are likely to have important influences on these concerns for the future sustainability and quality of healthcare in Europe. Whereas some of them will be more or less pre-determined and inevitable, others can be influenced and impacted upon by RTD and health policy makers. In the present context we have identified two factors or domains which are regarded as core for the direction of the scenarios to be developed:

a) Health system structure and healthcare delivery processes: move towards a more collaborative health system organisation and *integrated service provision* to allow our health systems to better meet and cope with the identified challenges.

By integrated health services, we refer to the overall working definition put forward by the World Health Organisation:[43] "The management and delivery of health services so that clients receive a continuum of preventive and curative services, according to their needs over time and across different levels of the health system."

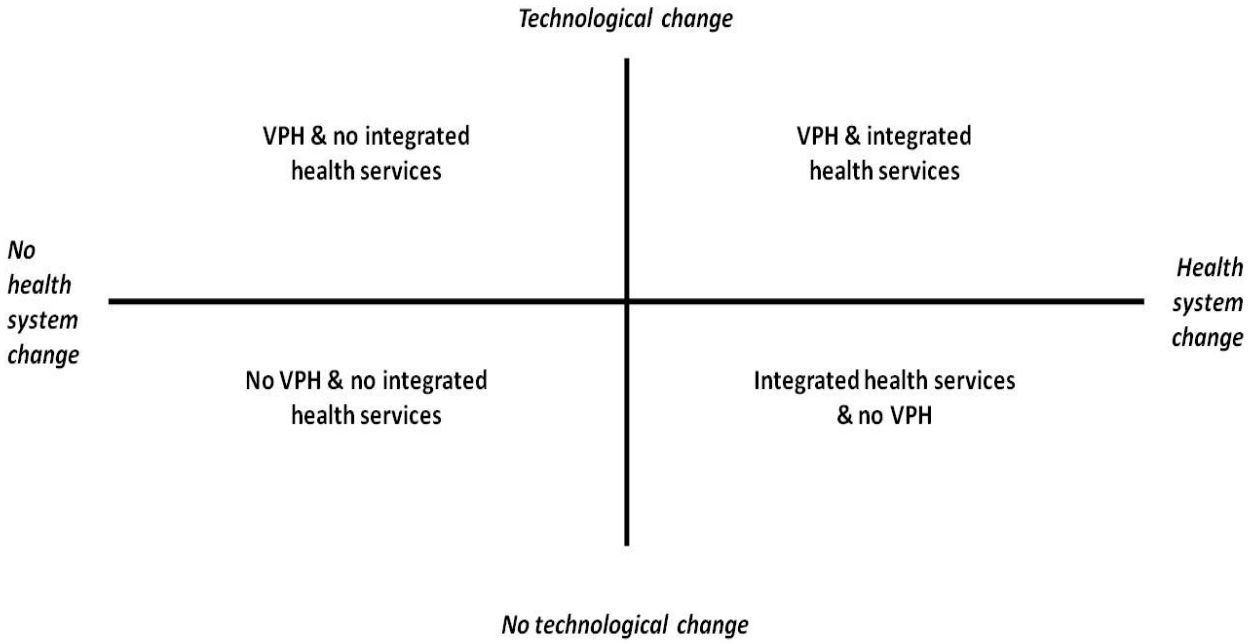
b) Investment in the facilitating and enabling capacities of advanced health ICT technology systems and applications: For our purposes, investment particularly in *VPH tools and services* is expected to contribute, in the longer run, fundamentally to and put medical progress into the clinical context to improve prevention and diagnosis of diseases, and to facilitate the prediction of the likely impact of a given clinical intervention, thereby helping to reduce treatment costs and optimise overall benefits to society.

By identifying these two critical factors as the central themes of our scenarios and by applying the so-called deductive, 'axes of uncertainty' approach leads to a scenario logic or scenario plot as illustrated by the following graph:

[42] Stroetmann, K.A. (2012). "Achieving the integrated and smart health and wellbeing paradigm: A call for policy research and action on governance and business models." International Journal of Medical Informatics. Stroetmann, K.A., et al. (2010). How can telehealth help in the provision of integrated care?, World Health Organization. Regional Office for Europe

[43] WHO, *Integrated Health Services - What and Why? Technical Brief No.1*, 2008.

FIGURE 5: SCENARIO PLOTS OF THE DRIVING FORCES 'MOVING TOWARDS INTEGRATED SERVICE PROVISION' AND 'INVESTMENT IN VPH TOOLS AND SERVICES'



This methodological approach renders one generic potential scenario story for each of the quadrants; a total of 4 overall.

Scenario 1: Status quo, no progress in either the domain of integrated health service delivery or of VPH tools and services

Current health systems have, for a wide variety of reasons, failed to adapt to and meet old and new challenges, and take advantage of new opportunities. Despite increases in funding, healthcare systems are still largely inefficient, fragmented and wasteful. They are unable to re-engineer and move forward.

ICT-based health innovations fail to diffuse, most fail, and VPH-based tools and systems are not widely supported, not to mention implemented and widely applied.

This scenario is unlikely despite the significant inertia of some health systems, and, in any case, this has no relevance to our present context, and thus will not be pursued further.

Scenario 2: Focus on ICT/VPH technology progress only

On a health systems level, this scenario follows the same underlying premise as scenario 1: Current systems are still largely inefficient and fail to adapt to new challenges.

However, technical innovations and investment in their diffusion, particularly those making use of advanced ICT technologies, become a key driver for positive change. This applies in particular to investments in *VPH tools and services*. Four core clinical applications can be identified underpinning the value proposition for investment in VPH technologies:

1. Screening and prevention: VPH-based tools and services will supplement, or even replace, conventional screening for patients at risk of developing a given disease, thereby significantly improving the correct identification of patients potentially at risk, in need of more detailed examination, and/or requiring preventive measures.
2. Diagnosis: VPH-based tools and services will allow a personalised assessment of the risk of a certain disease or its likely progression to be undertaken, thereby permitting improved identification of those in need of immediate treatment, of those who should be re-screened after a certain time period, and of those who should not (unnecessarily) be treated.
3. Prognosis: For patients at (high) risk of a disease, they provide a predictive model that estimates the variation of such risks over time, e.g., with/without certain pharmacological treatment options, interventional procedures etc.
4. Intervention/treatment planning and support: VPH modelling outcomes allow for improved pre-intervention/pre-operative planning to decide where and how an intervention may be executed with the lowest risk, which type of intervention would be most effective, and to estimate the reduction of the risk of disease progression that the treatment produces.
5. Supporting the need for patient to be fully informed about the procedure that they consent to and to any associated risks, leading to a better patient experience and reduced risk of litigation.

Such developments are expected to contribute fundamentally, in the long run, to improved prevention and diagnosis of disease, and will facilitate the prediction of the likely impact of a given clinical intervention, thereby reducing treatment costs and optimise overall benefits to society. In this way, VPH-based technologies support the achievement of change in a system with limited resources by focusing on cost-saving and productivity-increasing technologies.

This scenario will be pursued further as it has a certain likelihood as well as great relevance in the present context.

Scenario 3: Focus on integrated service provision only, no progress in the domain of VPH tools and services

This scenario assumes that our health systems will, at least in the longer term, adapt to and become enabled to meet old and new challenges, and to take advantage of new opportunities. Healthcare systems will become less inefficient, fragmented, and wasteful, and will move towards re-engineering healthcare structures and delivery processes. This will result in a more collaborative health system organisation and integrated service provision to allow our health systems to better meet, and cope with, the identified challenges.

In common with scenario 1, ICT-based health innovations fail to diffuse, rather most of them fail, and VPH-based tools and systems, are not widely support, not to mention implemented and widely applied.

We believe that such a scenario is not very likely and, due to the missing technological dimension. It is of no relevance to our present context, and therefore will not be pursued further.

Scenario 4: Focus on moving towards integrated service provision and investment in VPH tools and services

This scenario combines aspects of scenarios 2 and 3. Such an integrative approach towards health system adaptation to present and future challenges through moving towards integrated service provision as well as investment in ICT systems and applications, particularly VPH tools and services may seem as the best of both worlds.

Whether such a development is very likely or not is difficult, if not impossible, to judge reliably at this juncture. However, it will be highly relevant for the future development and potential clinical impact of VPH applications, and therefore this scenario will also be pursued further.

In summary, we strongly suggest in future work to pursue the further development and exploration of just two of the potential four scenarios, namely:

A) Focus on ICT/VPH technology progress only

B) Focus on moving towards integrated service provision *and* investment in VPH tools and services.

7.5. Measuring socio-economic impact

In order to render the scenarios to be developed useful and reasonably realistic, it will be necessary to provide at least rough estimates of their potential socio-economic impact, and in particular their clinical benefits. The major *stakeholders* to be considered will be citizens/patients, healthcare providers, and society at large. The latter represent societal value beliefs which are particularly relevant in a field such as health.

7.5.1. Clinical impact and benefits

Clinical impact and health-related outcomes may refer to factors and variables such as:

- Primary and secondary endpoints of medical and clinical trials, for example, changes in mortality (death rate) or morbidity (disease rate), length of stay in hospital, visits to physicians/outpatient clinics or hospitals avoided, quality of life of patients, etc.

Other benefits may include

- Reduced period of bed-rest at home for patients, reduced readmission rates due to the avoidance of complications and side effects, fewer drugs to take, less care to be provided by community nurses, family carers and neighbours, fewer side-effects experienced, etc.

Further clinical impacts may relate to

- Organisational and change management aspects
- Human resource implications, knowledge & education needs
- Efforts for application (convenience/ease of use; costs for introduction of new technology)

In our further scenario development and the estimation of clinical impacts the focus will be predominantly on factors and measurements related to the first two bullets points above because, in the long-term, highly uncertain context they are regarded as of primary interest and relevance. Only if clear benefits in terms of factors of immediate impact on the health and well-being of patients are to be expected, do further factors important for the successful implementation and diffusion at the clinical level of such new approaches become relevant.

7.5.2. Cost considerations and the business case

Assessing whether a certain scenario may indeed constitute a likely business case for a healthcare provider organisation or society at large, i.e. can be expected to eventually reach clinical workflow level, also requires at the very least a ball-park assessment of costs for implementing the workflow, infrastructure- and organisation-related costs; and, where feasible, the implied organisational burden of changing current standard of care pathways.

Generic relevant factors and variables include:

- Upfront investment expenditures/(depreciation) costs into
  - ✓ databases
  - ✓ computer-hardware
  - ✓ software
  - ✓ training of professionals and technicians
- Running costs for
  - ✓ databases
  - ✓ computer-hardware
  - ✓ software
  - ✓ (re-)training of professionals and technicians
  - ✓ personnel involved in delivering and supporting the VPH workflow (such as medical professionals, technicians, other personnel)
  - ✓ general overhead.
- Affordability is another intervening variable to be considered.

Of course, the longer the time horizon applied – we assume that a 10 to 15 year horizon will be meaningful – the more uncertain any estimate of future costs becomes. Nevertheless, including such considerations will allow initial discussion of certain factors which may need particular attention during the further development cycles of the technology under consideration so as to improve the likelihood of indeed realising a realistic business case.

8. Conclusions

Through newly developed clinical pathways, the transformation of bio-computational modelling and VPH technologies into a future patient flow are meant to supplement and improve the current management the specific diseases targeted by MD-Paedigree. The VPH technology assessment framework developed and proposed in this deliverable will force many of the implicit assumptions behind such developments to lay bare. Since the assessment perspective is to develop concrete clinical scenarios, the further work on the MD-Paedigree technologies will clearly benefit from a much more focused alignment towards producing results that matter within the context of deployable, routine clinical applications.

Whereas verification and validation of simulation models relate to their technical merit (is it feasible/does it "work"?), a clinical and socio-economic assessment perspective facilitates the development and testing of clinical application scenarios for bio-computational models.

For evidence-informed implementation and diffusion decisions, conventional HTA-based efficacy assessments need to be complemented by dynamic benefit-cost modelling. This must also consider and reflect value-propositions for key stakeholders involved, thereby supporting health policy decision making and allowing for the development of successful business models. In other words, the application of the developed framework and approach will deliver support tools as well as empirical evidence for

- health system actors & decision makers,
- exploitation planning,
- business modelling.