# Assessment element tables for HTA Core Model Application for Pharmaceuticals (2.1)

## Contents

## 1 Health Problem and Current Use of the Technology

| ID | Topic | Issue | Clarification | Import. | Transf. | Is core | Methodology | Content relations | Sequential relations | References |
|---|---|---|---|---|---|---|---|---|---|---|
| A0007 | Target Population | What is the target population in this assessment ? | Relevant for all assessments: both safety and effectiveness depend largely on the subpopulation towards which the intervention is targeted. The technology may be used for all patients with the condition, or only those in the early stages, or at a specific severity level, or for those at moderate risk of having the condition.<br><br>Personalised medicine divides the target population into even smaller units when targeting the intervention to specific subgroups based on e.g. genetic profile. Use the target population defined in the scope of the project, and consider adding further details and description of who defined the selected subgroups and why.<br><br>Point out e.g. if certain populations should be excluded from the analysis. | Critical | Partial | Yes | Sources: HTAs, guidelines, reviews, developers/manufacturers. Method: A descriptive summary. | | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |
| A0023 | Target Population | How many people belong to | This information can be used to give an idea of the | Critical | Partial | Yes | Sources: text books, HTAs, | | | Burls 2000 {1}, Velasco 2002 {25}, Liberati 1997 |

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| | | the target population? | resource requirements in general for implementing the technology. Estimates of likely relevant increases or decreases in the size of the target population in the future should also be included. | | | | national registries, statistics, systematic reviews. Method: A descriptive summary. | | | {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |
| A0002 | Target Condition | What is the disease or health condition in the scope of this assessment ? | Use the target condition and ICD codes defined in the scope of the project and consider adding details such as: description of anatomical site, disease aetiology and pathophysiology, types of disease or classification according to origin, severity, stages, or risk level, and different manifestations of the condition. The following properties of the target condition are defined in separate assessment elements: risk factors (A0003), natural course (A0004), symptoms (A0005), and burden of disease for the society (A0006). | Critical | Complete | Yes | Sources: text books, HTAs, guidelines, epidemiological reviews or studies, WHO documents, disease registers. Method: A descriptive summary. | | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |
| A0003 | Target Condition | What are the known risk factors for the disease or health condition? | Describing risk factors is especially important when they suggest possibilities for primary and secondary prevention. This information may affect the choice of | Important | Partial | Yes | Sources: text books, HTAs, guidelines, epidemiological reviews or studies. | | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |

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| | | | comparator or the appraisal of the overall value of the technology under assessment. The risk factors for acquiring the condition, and the risk factors for relapses or worsening of the condition should be reported here, separately. The prevalence of the various risk factors might differ in different geographic areas and among different sub-populations. | | | | Method: Systematic review is generally not required. A descriptive summary is sufficient. | | | |
| A0004 | Target Condition | What is the natural course of the disease or health condition? | This assessment element should provide information on the prognosis and course of the condition when untreated. This information is relevant for appraising the overall value of the technology. A technology targeted to cure a life-threatening condition has a different significance from a technology intended to alleviate the symptoms of self-limiting conditions. It may also guide the assessment of the predicted value or effectiveness of the technology, as technologies may work differently at different stages or severity grades of the disease, and there may be a relationship between earlier intervention and better prognosis. This | Critical | Complete | Yes | Sources: text books, HTAs, guidelines, epidemiological reviews or studies.<br>Method: A descriptive summary. | | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |

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| | | | element should also provide information on the time lag between the onset of disease and the symptoms or other findings that eventually trigger the need of diagnostics and care. | | | | | | | |
| A0005 | Target Condition | What are the symptoms and the burden of disease or health condition for the patient? | Describe the patient's relevant symptoms before intervention with the technology, their severity and whether they are persistent, intermittent, or undulating, taking into account different stages of the disease. Patients' perceptions of the burden of the disease are not always in line with the clinical seriousness of the disease or its societal burden.<br><br>This issue is especially relevant when the patient or individual is expected to undergo a substantial change in pain, disability, psychosocial issues, or other determinants of quality of life.<br><br>Knowing the severity level of the condition the technology is directed to is relevant in the ethical analysis of the technology. Information about the severity level is also important to decision-makers | Critical | Complete | Yes | Sources: text books, HTAs, quality of life studies, qualitative patient perception studies.<br>Method: A descriptive summary. | | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |

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| | | | when making decisions about whether or not to implement a technology. | | | | | | | |
| A0006 | Target Condition | What are the consequences of the disease or health condition for the society? | Describe consequences and burden of the disease or health condition by providing information on prevalence or incidence of the disease that is prevented or treated by using the technology; disease-specific mortality and disability, life years lost and/or disability-adjusted life years, quality of life, QALYs. | Critical | Partial | Yes | Sources: text books, HTAs, registries and national statistics, WHO incidence, mortality and survival databases.http://www.who.int/cancerc/resources/incidences/en/ Method: A descriptive summary | | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |
| A0009 | Target Condition | What aspects of the consequences / burden of disease are targeted by the technology? | The technology can affect only some aspects (e.g. mortality) and leave other aspects (e.g. quality of life) untouched. | Critical | Complete | Yes | Deductive models (based on the natural history of the disease, test target and treatment target; epidemiological studies (if sufficient testing has been done). | B0002 | | |

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| A0017 | Current Management of the Condition | What are the differences in the management for different stages of the disease or health condition? | Identification of practice variations due to the differences in the forms, stages or severity of the disease. May be useful to understand the proper place of technology in the health care delivery process.<br><br>Different stages of disease may call for different therapeutic procedures (for example aortic insufficiency is first treated with medication and at a certain point of cardiac structural changes an operation is preferred).<br><br>Provide an overview of other treatment alternatives. Likewise diagnostic or monitoring methods used for various diseases may vary depending on the stage of disease.. | Critical | Partial | Yes | Surveys, utilisation reviews, clinical guidelines, recommendations. If such information is lacking: expert surveys / expert interviews | | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |
| A0018 | Current Management of the Condition | What are the other typical or common alternatives to the current technology? | Provide an overview of other treatment alternatives. Focus primarily on those used within professional health care delivery. Consider including technologies that people may commonly seek or use even if these wouldn't be commonly provided in professional health care (e.g. | Critical | Partial | Yes | Clinical guidelines, recommendations, systematic reviews | B0001 | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |

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| | | | technologies for self-testing or self-treatment, or alternative medicine). | | | | | | | |
| A0024 | Current Management of the Condition | How is the disease or health condition currently diagnosed according to published guidelines and in practice? | The effectiveness of an intervention may vary in differently diagnosed populations. A sensitive test tends to have low specificity such that there are several people who do not have the condition among the test-positive population. The effectiveness of an intervention in that population may be lower than in a population examined with a less sensitive test (but with more true positive cases). It is important to point out possible discrepancies between guidelines and actual practice. | Important | Partial | Yes | Sources: Clinical guidelines and published utilisation reviews; in the absence of these, clinical experts survey. See Appendix 1. Method: Systematic review of clinical guidelines. Quality appraisal of guidelines can be done using e.g. AGREE II Instrument. For practice mapping, a pragmatic review or listing of available information is sufficient. Flowcharts are illustrative in reporting diagnostic | | | Burls 2000 {1}, Velasco 2002 {25}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |

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| | | | | | | | pathways. | | | |
| A0025 | Current Management of the Condition | How is the disease or health condition currently managed according to published guidelines and in practice? | It is important to describe whether the technology is an add-on or a replacement for the existing management options, and what the other evidence-based alternatives are. Are there differences in the treatment of diseases at their different stages? Identification of practice variations may imply differences in the quality of health care. Deviation from evidence-based guidelines may suggest over/under use of the technology. | Critical | Partial | Yes | Sources: Clinical guidelines and published utilisation reviews; in the absence of these clinical experts survey. See Appendix 1. Method: Systematic review of clinical guidelines. Quality appraisal of guidelines can be done using e.g. AGREE II Instrument. For practice mapping, a pragmatic review or listing of available information is sufficient. Flowcharts are illustrative in reporting management pathways. | | | |

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| A0001 | Utilisation | For which health conditions and populations, and for what purposes is the technology used? | All relevant conditions and populations should be included. This question is especially relevant when there are multiple potential target conditions and populations for which the technology is used, and multiple intended uses, both indicated and other. There may also be differing views about the appropriate use of the technology that it is essential to highlight. Describe the differences in the use of the technology for the various indications and how it might act differently in different patient groups. Point out e.g. if certain populations should be excluded from using the technology, or if they require e.g. a different dosage. Certain technologies may be primarily indicated for second-line use but also used for first-line treatment. | Critical | Complete | Yes | Sources: HTAs, guidelines, reviews, clinician consultation, developers/manufacturers.<br><br>Method: A descriptive summary. | | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |
| A0011 | Utilisation | How much are the technologies utilised? | Provide national estimates for current and future utilisation rates, for the indication under assessment, for both the technology under assessment and its comparators. Variations in utilisation reflect market | Critical | Partial | Yes | National statistics, surveys, technology and procedure registers, disease management | G0009<br><br>G0010 | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |

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| | | | access, sales figures, actual usage in hospital level and adherence to the use of the technology by both professionals and patients. Data on current and previous utilisation reflect the phase of the technology (experimental, emerging, established or obsolete). This also has implications for the availability of evidence and the level of uncertainties. | | | | studies, utilisation studies, manufacturer sales data | | | |
| A0012 | Utilisation | What kind of variations in use are there across countries/regions/settings? | This information can be useful for decision-makers to understand regional variations in their own country and also understand the situation in comparison with other countries. | Important | Partial | Yes | National statistics, surveys, disease management studies, manufacturer sales data, utilisation reviews, audits, studies on praxis-variation. Own primary analysis of: Disease register, procedure register, device register, administrative data (DRG, dicharge | G0009<br><br>G0010 | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |

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| | | | | | | | databases, reimbursement claims database). | | | |
| G0009 | Utilisation | Who decides which people are eligible for the technology and on what basis? | Provide information on who are the key actors in deciding on the use of the technology. Do most important decisions take place on the national level (e.g. population screening) or for example by individual professionals (e.g. surgical method for a specific disease)? How is the decision made; are there some documented criteria?<br><br>Information about the possible variations in the decision level and criteria has ethical implications.<br><br>This issue is related to the issue of work processes (G0001)<br><br>Companion diagnostics (tests or measurements) assist physicians in making treatment decisions for their patients by elucidating the efficacy and/or safety of a specific pharmaceutical or class of pharmaceuticals for a targeted patient group or sub-groups. How companion | Important | Partial | Yes | Literature search, guidelines, documents of hospitals, own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory). | A0011<br><br>A0012<br><br>:B0016, D0021, F0012, I0012, H0012 | | Kristensen 2007 {24}<br><br>{14} |

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| | | | diagnotic should be used to identify eligible patient should be specified and explained.<br><br>Criteria must be specified for higher risk groups of patients such as elderly and children. | | | | | | | |
| B0003 | Utilisation | What is the phase of development and implementation of the technology and the comparator(s)? | Most technologies will be introduced at approximately the same time in several countries. This information is relevant for the assessment while the evidence base may change rapidly for technologies that are at an earlier stage in their development. It is also important to establish whether new versions of the technology with substantial improvements are expected in the near future. For end users it is useful to know if new versions or adaptations of the technology are expected in the near future.<br><br>Describe the following aspects:<br><br>- Is the technology an innovation?<br><br>-When was it developed?<br>-Is the technology only partially innovative (i.e. a | Critical | Partial | Yes | Manufacturers´ sites and effectiveness studies, HTAs, guidelines, published literature including reviews, textbooks, introduction sections of research articles, grey literature, hand-searches and conference proceedings. | A0020<br><br>A0021<br><br>A0011<br><br>A0019<br><br>A0020<br><br>F0001 | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24}<br><br>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005 |

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| | | | modification of an existing technology), and in that case, is it possible to specify the degree of innovation the technology may represent?<br>-When was the technology introduced into healthcare?<br>-Is the technology an already established one, but now used in a different way, for instance for a new indication?<br>-Is it experimental, emerging, established in use or obsolete (implementation level)?<br><br>- Is the technology field changing rapidly<br><br>-How does this technology differ from its predecessors (other technologies used for similar purposes)?<br>-Are there new aspects that may need to be considered when applying it?<br>-Is there evidence that the technology works (or is used) outside its current indication area or produces incidental findings that can have consequences relevant to effectiveness, safety, organisational, social and ethical domains. | | | | | | | |
| F0001 | Utilisation | Is the technology a new, | Explain how the possible use / non-use of the technology | Critical | Partial | Yes | Horizon scanning | | | Mitcham 2004 {26} |

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| | | innovative mode of care, an add-on to or modification of a standard mode of care or replacement of a standard mode of care? | would affect the current treatment process and practices. How substantial is the change to current practices?<br><br>Notice that the technology may be in a different phase of utilisation for different health conditions or purposes of use. | | | | databases, ongoing research databases, information from manufacturers. | | | |
| A0020 | Regulatory Status | For which indications has the technology received marketing authorisation or CE marking? | There are both international and national market authorisation systems. For pharmaceuticals the systems are established but for devices and procedures less so. An overview of the status with regard to key processes, e.g. CE marking, EMA/FDA approval is recommended. Also information on national data and an analysis of possible discrepancies can be highly useful. | Critical | Complete | Yes | CE-Approval, EMA, FDA, national authorities. Manufacturers should be contacted in order to identify which steps have they taken/ are they planning to take concerning market approval | I0015<br><br>B0002 | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |
| A0021 | Regulatory Status | What is the reimbursement status of the technology? | Information on national reimbursement status from different countries for the technology as well as the comparators, including key | Important | Complete | Yes | Appendix 1 of REA model = List of websites of national agencies with | I0012<br><br>B0002 | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |

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| | | | dates and anticipated licensing timeframe should be listed here. Notice that reimbursement status may differ for different purposes: e.g. treatment vs. prevention. Information on full coverage, co-payments, coverage under special circumstances/conditional coverage is useful. | | | | information on reimbursement ,<br><br>EVIDENT database. | | | |

## 2 Description and technical characteristics of technology

| ID | Topic | Issue | Clarification | Import. | Transf. | Is core | Methodology | Content relations | Sequential relations | References |
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| B0001 | Features of the technology | What is this technology and the comparator(s)? | This is relevant in all assessments. Use the descriptions of the technology and comparator(s) defined in that scope and elaborate them here in more detail. Technology may include a single device, a questionnaire, imaging or sequence of technologies. The HTA may address one or several similar technologies.<br><br>Describe separately for the technology and the comparator: the type of device, technique, procedure or therapy; its biological rationale and mechanism of | Critical | Complete | Yes | Manufacturers´ sites, published literature including reviews, textbooks, introduction sections of research articles, effectiveness studies, clinical experts, studies in basic science, HTA-reports. | A0022<br><br>A0018<br><br>F0001 | | Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005 |

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| | | | action, and also, describe how the technology differs from its predecessors, and the various current modifications or different manufacturers' products, especially if the dissimilarities affect performance. | | | | | | | |
| B0002 | Features of the technology | What is the claimed benefit of the technology in relation to the comparators? | This issue is especially relevant in new technologies with uncertain expectations and claims of benefit.<br><br>Describe the following aspects:<br><br>-How is it expected to be an improvement over previous /existing technologies used for the same health problem?<br>-The expressed objectives for the implementation of the technology in health care; what are the claimed objectives e.g. increased safety, health benefit, accuracy or patient compliance, and whether it is intended to replace or to supplement existing technologies. Is the technology licensed as a mono-intervention, or in addition to current interventions (which should be specified) Are there | Critical | Partial | Yes | Manufacturers´ sites, HTAs, effectiveness studies, clinical experts, published literature including reviews, introduction sections of research articles, grey literature, hand-searches and conference proceedings, consulting clinical professionals, lay journals and websites. | A0001<br><br>A0009<br><br>C0008 | | Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005 |

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| | | | stopping rules for use of the technology? Is there evidence that the technology works (or is used) outside its current indication area, or produces incidental findings that can have consequences relevant to effectiveness, safety, organisational, social and ethical domains? This information may explain the choice of comparator(s) and outcomes for the assessment and helps in appraising the overall results. | | | | | | | |
| B0003 | Features of the technology | What is the phase of development and implementation of the technology and the comparator(s)? | Most technologies will be introduced at approximately the same time in several countries. This information is relevant for the assessment while the evidence base may change rapidly for technologies that are at an earlier stage in their development. It is also important to establish whether new versions of the technology with substantial improvements are expected in the near future. For end users it is useful to know if new versions or adaptations of the technology are expected in the near future.<br><br>Describe the following | Critical | Partial | Yes | Manufacturers´ sites and effectiveness studies, HTAs, guidelines, published literature including reviews, textbooks, introduction sections of research articles, grey literature, hand-searches and conference proceedings. | A0020<br><br>A0021<br><br>A0011<br><br>A0019<br><br>A0020<br><br>F0001 | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24}<br><br>Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005 |

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| | | | aspects:<br><br>- Is the technology an innovation?<br><br>-When was it developed?<br>-Is the technology only partially innovative (i.e. a modification of an existing technology), and in that case, is it possible to specify the degree of innovation the technology may represent?<br>-When was the technology introduced into healthcare?<br>-Is the technology an already established one, but now used in a different way, for instance for a new indication?<br>-Is it experimental, emerging, established in use or obsolete (implementation level)?<br><br>- Is the technology field changing rapidly<br><br>-How does this technology differ from its predecessors (other technologies used for similar purposes)?<br>-Are there new aspects that may need to be considered when applying it?<br>-Is there evidence that the technology works (or is used) outside its current indication area or produces incidental | | | | | | | |

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| | | | findings that can have consequences relevant to effectiveness, safety, organisational, social and ethical domains. | | | | | | | |
| B0004 | Features of the technology | Who administers the technology and the comparators and in what context and level of care are they provided? | Describe the following aspects:<br><br>-Which professionals (nurses, doctors, and other professionals) apply and make decisions about starting or stopping the use of the technology?<br>-Do the patients themselves, or their carers, administer the technology?<br>-Who can select the patients, make referrals, decide to initiate the use of the technology, or interpret the outcome?<br>-Are there certain criteria (skills, function, training requirements) for the patients or professionals who will administer the technology?<br><br>Describe the level of care in which the technology is used: self care, primary care, secondary and tertiary care. If secondary or tertiary care, describe whether it is intended to be used in the outpatient or inpatient setting. | Critical | Partial | Yes | Clinical guidelines, professionals' consensus statements, HTAs, manufacturers´ websites, introduction sections of research articles, interviews with clinical professionals or patients.<br><br>Manufacturer, effectiveness studies, clinical experts, legislation. National or local judgement, as well as grey literature, hand-searches and conference proceedings can be also | Current use, organizational A0012 A0025 G001 G0005 | | Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005 |

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| | | | Its role in the management pathway can be as a replacement, an add-on or for triage | | | | used. | | | |
| A0020 | Regulatory Status | For which indications has the technology received marketing authorisation or CE marking? | There are both international and national market authorisation systems. For pharmaceuticals the systems are established but for devices and procedures less so. An overview of the status with regard to key processes, e.g. CE marking, EMA/FDA approval is recommended. Also information on national data and an analysis of possible discrepancies can be highly useful. | Critical | Complete | Yes | CE-Approval, EMA, FDA, national authorities. Manufacturers should be contacted in order to identify which steps have they taken/ are they planning to take concerning market approval | I0015<br><br>B0002 | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |
| A0021 | Regulatory Status | What is the reimbursement status of the technology? | Information on national reimbursement status from different countries for the technology as well as the comparators, including key dates and anticipated licensing timeframe should be listed here. Notice that reimbursement status may differ for different purposes: e.g. treatment vs. prevention. Information on full coverage, co-payments, coverage under special | Important | Complete | Yes | Appendix 1 of REA model = List of websites of national agencies with information on reimbursement,<br><br>EVIDENT database. | I0012<br><br>B0002 | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |

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| | | | circumstances/conditional coverage is useful. | | | | | | | |
| B0007 | Investments and tools required to use the technology | What material investments are needed to use the technology? | Devices, machinery, computer programs, etc. Those parts of the technology that need to be purchased (and often installed) by an organisation in order to use the technology. Includes need for back-up investment to cover for breakdowns in use. | Important | Partial | Yes | Manufacturers´ sites, published literature including reviews, textbooks, handbooks, introduction sections of research articles, interviews with specialists, clinical experts, user information. National or local judgement, as well as grey literature, hand-searches and conference proceedings. | E0001<br>E0002<br>G0006<br>G0003? | | Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005 |
| B0008 | Investments and tools required to use the technology | What kind of special premises are needed to use the technology and the | Many technologies require purpose-built premises, such as radiation-secured areas, Faraday cages, dressing rooms for the patient, or specific premises for storage | Critical | Complete | Yes | Sources: User information from manufacturer, and market approval | | | Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005 |

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| | | comparator(s)? | and reconstitution of chemotherapy pharmaceuticals equipped with fume cupboards.<br><br>Typical premises in primary or secondary care may differ markedly from country to country.<br><br>A clear description of necessary facilities is needed instead of general statement (e.g. to be used in hospitals only) | | | | authority. HTAs, applicability studies, interviews with clinical experts and hospital managers.<br><br>Manufacturer, applicability studies, clinical experts, user information. National or local judgement can be also used. | | | |
| B0009 | Investments and tools required to use the technology | What equipment and supplies are needed to use the technology and the comparator? | Describe all required disposable items necessary for using the technology, such as: syringes, needles, pharmaceuticals and contrast agents, fluids, bandages and tests to identify patients eligible for treatment. | Critical | Complete | Yes | Sources: Information from manufacturer, HTAs, applicability studies, interviews with clinical professionals and hospital managers.<br><br>Manufacturer, applicability studies, clinical experts, user information. | E0001<br><br>E0002<br><br>G0006 | | Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005 |

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| | | | | | | | National or local judgement can be also used. | | | |
| B0010 | Investments and tools required to use the technology | What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator? | Describe the data that needs to be collected about the care process, professionals involved, patients and their health outcomes. These include: e.g. clinical indications, specified populations, prescriber information, inpatient or outpatient use, test results, review period, and health outcomes. In case of new technologies, consult EVIDENT database.<br><br>Describe the general importance of having a registry to monitor the use of this particular technology and the comparator. Are there existing registries that should be used, or should a registry be established, to collect the necessary data to monitor safety or true life effectiveness? Provide national examples.<br><br>Refer to SPC and EPAR.<br><br>Sometimes registries are connected with the risk | Critical | Partial | Yes | Sources: Local authorities and legislation, administrative staff, clinical professionals, HTAs, National or local judgement. | G0008<br><br>G0003 | | Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005 |

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| | | | sharing scheme that innovative pharmaceuticals require in some countries. Notice also the requirements of pharmacovigilance monitoring. | | | | | | | |
| B0012 | Training and information needed to use the technology | What kind of qualification and quality assurance processes are needed for the use or maintenance of the technology? | Differentiate between the users who are. 1. applying the technology (could be different from those interpreting results) 2. interpreting the results and make clinical decisions. 3. taking care of service and maintenance.<br><br>Describe what type of training materials (writing and/or translation, other adaptation) and the characteristics of the personal training (individual and/or group sessions, number and length of sessions, number and qualifications of trainers) and if regular or frequent standardisation or quality checks are required (E.g. CME points). Provide an estimate to what extent the training and quality assurance measures may affect the efficacy and safety of the technology. | Critical | Partial | Yes | Manufacturers´ sites, approving authority, published literature including handbooks, textbooks, reviews, HTA-reports, interviews with specialists and clinical experts, as well as grey literature, hand-searches and conference proceedings.<br><br>Research studies and national or local judgement can be used. | G0003<br><br>C0020<br><br>C0062<br><br>C0063<br><br>E0001<br><br>E0002<br><br>G0006 | | Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005 |

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| B0013 | Training and information needed to use the technology | What kind of training and information is needed for the personnel/carer using this technology? | Describe what type of training materials (writing and/or translation, other adaptation) and the characteristics of the personal training (individual and/or group sessions, number and length of sessions, number and qualifications of trainers); if the technology requires a specific skill that is developed over a period of time using the technology (learning curve), an estimate should be provided of the number of patients a professional needs to treat (as a basis or per year) in order to reach an acceptable minimum standard. Provide an estimate to what extent the training and quality assurance measures may affect the efficacy and safety of the technology. | Important | None | No | Manufacturer, effectiveness studies, observational studies, applicability studies, clinical experts, user information, HTA-reports. National or local judgement. | G0003<br>C0020<br>C0062<br>C0063<br>I0008<br>F0006 | | Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005 |
| B0014 | Training and information needed to use the technology | What kind of training and information should be provided for the patient who uses the technology, or for his | Describe what type of training materials should be provided (writing and/or translation, other adaptation) by whom, and the characteristics of the personal training (individual and/or group sessions, number and length of sessions, number and qualifications of trainers) and | Optional | None | No | Manufacturer data, effectiveness studies, observational studies, applicability studies, clinical experts, user information, | C0008<br>C0003<br>C0005<br>C0007<br>C0062 | | Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005 |

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| | | family? | if the informed consent regarding the risk/benefits of participation is required. | | | | patient organisations, HTA-reports.<br><br>National or local judgement | F0004<br><br>F0006<br><br>G0004<br><br>H0003<br><br>H0007<br><br>H0008<br><br>I0002 | | |
| B0015 | Training and information needed to use the technology | What information of the technology should be provided for patients outside the target group and the general public? | Describe what type of information materials should be provided (writing and/or translation, other adaptation) and if the informed consent for participating is required? | Optional | None | Yes | Manufacturer data, effectiveness studies, observational studies, applicability studies, clinical experts, user information, patient organisations, HTA-reports, discussion forums in web, as well as grey literature, hand-searches and conference proceedings,<br><br>National or | F0005<br><br>F0011<br><br>G0004<br><br>H0002<br><br>H0007<br><br>H0008<br><br>I0002<br><br>I0008 | | Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005 |

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| | | | | | | | local judgement | | | |
| A0022 | Other | Who manufactures the technology? | | Important | Partial | Yes | Manufacturers´ information, clinical guidelines, legislation, HTAs, approving authority, National or local judgement. | Related to Organisational domain | I0037 | Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005 |

## 3 Safety

| ID | Topic | Issue | Clarification | Import. | Transf. | Is core | Methodology | Content relations | Sequential relations | References |
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| C0008 | Patient safety | How safe is the technology in relation to the comparator(s)? | Here one should identify and describe the direct harms of the use and the administration of the technology and the comparator(s). Highlight the differences in the most important risks (i.e. the most severe and frequent harms) of the technology and its comparator(s). For harms that are common to both the technology and the comparator(s), provide information on which has the higher risk of the particular harm. Aspects of individual patients, populations, service delivery & cost effectiveness should be considered.<br><br>User-dependent harms are described in C0007. Harms are identified in placebo-controlled trials, observational studies, and in registries. It is important to refer to the source and report separately harms identified in spontaneous reporting databases. Harms should be reported per indication or | Critical | Partial | Yes | Placebo controlled trials, observational research, FDA database, safety monitoring databases, observational research, registers, statistics registers, statistics, research articles, manufacturers' product data sheets.<br><br>Other HTA reports or systematic reviews of main comparators.<br><br>Method: Systematic review. Results should be | B0001<br><br>A0018<br><br>D0009; D0003<br>A0001<br>A0007 | B0001<br><br>A0018<br><br>A0001<br><br>A0007 | { 1, 12 ,14, 16, 28, 29, 34, 37 } |

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| | | | target population . The identified harms should be categorised according to their severity and frequency. The seriousness of harm is typically graded based on events that pose a threat to a patient's life or functioning. Frequency of the occurrence of each harm is usually presented in comparison with placebo or no treatment, as percentages or risk ratios. Finally, the harms should be grouped by their severity and frequency and ordered so that the severe and/or frequent harms are presented first. If there are many different harms reported in the literature, concentrate on reporting the most serious and the most frequent harms<br><br>The important identified and potential adverse events/reactions presented in Risk Management Plan of the pharmaceutical (RMP) should be considered, as well as the important identified and potential interactions with other medicinal products, foods and other substances, and the important pharmacological class effects. | | | | presented by risk level (i.e. the product of severity and frequency of harm). | | | |

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| | | | Special attention should be given to drug interactions. Information in the label warnings and PSUR should be evaluated using literature and registration data.<br><br>Distinction should be made between absolute and relative contra-indications of the pharmaceutical use for particular patient groups co-medications. Co-medication should be understood in its largest way: not only medically prescribed pharmaceuticals but also over-the-counter pharmaceuticals such as non-steroidal anti-inflammatory pharmaceuticals, and herbal remedies.<br><br>Attention should be paid to the possibility of medication errors. Errors may be classified into near-miss events, no-harm events, and sentinel events. Cases of accidental overdose may be described in the EPAR but errors may also be related to the route of administration, storage conditions, reconstitution aspects, dosage, too long/too short treatment durations, or | | | | | | | |

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| | | | replacement of two pharmaceuticals which look alike or difficulties of handwriting readings that lead to mistakes by patient or professional.<br><br>For further information see Endpoints used in REA of pharmaceuticals – Safety http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Safety.pdf | | | | | | | |
| C0002 | Patient safety | Are the harms related to dosage or frequency of applying the technology? | Information should be included if safe use of the technology is sensitive to even small changes of the dose because this may have implications for the training and organisation of care. The potential for accumulated harm due to repeated dosage or testing should also be considered.<br><br>For further information see Endpoints used in REA of pharmaceuticals – Safety<br><br>http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Safety.pdf | Critical | Complete | Yes | Phase 1 studies for pharmaceuticals, other research articles, HTAs, manufacturers' product data sheets, safety monitoring databases. Method: Systematic review. | A0017<br><br>B0001 | A0017<br><br>B0001 | { 2, 11 } |
| C0004 | Patient safety | How does the frequency | This issue is especially relevant for new or evolving | Critical | Partial | Yes | Sources: HTAs, efficacy | Current use, | B0004 | |

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| | | or severity of harms change over time or in different settings? | technologies where there are considerable uncertainties in the safety evidence, and in technologies with steep learning curves. How does the safety profile of the technology vary between different generations, approved versions or products? Is there evidence that harms increase or decrease in different organisational settings? | | | | and safety research articles, articles on learning curve, manufacturers' information. Method: Descriptive summary. | effectiveness (D0001; D0008; D0009) , costs domains<br><br>B0004<br><br>B0001 | B0001 | |
| C0005 | Patient safety | What are the susceptible patient groups that are more likely to be harmed through the use of the technology? | Typically, people with comorbidities and co-medication, pregnancy, intolerances, or specific genetic profiles, elderly people, children and immunosuppressed patients. Are there any relevant contra-indications or interactions with other technologies? | Critical | Complete | Yes | HTAs, guidelines, market access authorities, manufacturers' product information, label warnings, safety monitoring databases. Method: Descriptive summary. | Ethical, Effectiveness domain (D0008;D0009)<br><br>B0016<br><br>B0001 | B0016<br><br>B0001 | { 2, 11 } |
| C0007 | Patient safety | Are the technology and comparator(s) associated with user-dependent | Describe here what is known of the harms caused by the properties or behaviour of professionals, patients or other individuals who apply or maintain the technology. Is there e.g. a noteworthy risk of | Critical | Partial | Yes | Sources: Studies on effectiveness, safety and health services research; manufacturers' | Description and technical characteristics and Organisational | B0006<br><br>B0001 | { 2, 11 } |

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| | | harms? | malfunction of a device, due to deficient user training or personal attitude; or a risk of errors related to reconstitution, dosage, administration, or storage of medicines, that may have serious consequences; or, is there a risk of addiction? Describe what is known of the learning curve, intra- or inter-observer variation in interpretation of outcomes, errors or other user-dependent concerns in the quality of care.<br><br>For further information see Endpoint used in REA of pharmaceuticals – Safety. http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Safety.pdf | | | | product data sheets, safety monitoring databases, label warnings. Method: Systematic review | domains B0006<br><br>B0001 | | |
| C0020 | Occupational safety | What kind of occupational harms can occur when using the technology? | Consider if there are possible harms to professional applying the technology: working positions, radiation or infection risks, etc. | Important | Complete | Yes | Research articles, manufacturers' product data sheets, safety monitoring databases | Ethical and Social domains<br><br>B0012<br><br>B0013 | B0012<br><br>B0013 | |
| C0040 | Environmental safety | What kind of risks for public and environment may occur | Several chemical substances or their toxic metabolites are potentially harmful in ecological environments; | Optional | Partial | No | Research articles, manufacturers' product data | Ethical and Social domains | | |

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| | | when using the technology? | some of the most recent concerns are endocrine modulators and disruptors and nanoparticles. The statistical risk of radiation at the public level should also be described here. | | | | sheets, safety monitoring databases<br><br>Method: Systematic review. | | | |
| C0060 | Safety risk management | How does the safety profile of the technology vary between different generations, approved versions or products? | | Important | Complete | Yes | Research articles, manufacturers' product data sheets, safety monitoring databases | Description and Technical Characteristics | | |
| C0061 | Safety risk management | Can different organizational settings increase or decrease harms? | | Critical | Partial | Yes | Research articles, manufacturers' product data sheets, safety monitoring databases. Descriptive review on accuracy and effectiveness research, epidemiological risk research | Current use, Effectiveness (D0009; Organisational<br><br>B0020<br><br>A0012 | B0020<br><br>A0012 | |

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| C0062 | Safety risk management | How can one reduce safety risks for patients (including technology-,user-, and patient-dependent aspects)? | Is there a requirement for specific training, use of a protocol or available guideline which may reduce the occurrence or severity of the harm.<br><br>Information on what kind of risk communication is needed for patients, citizens and decision makers may be included. | Important | Partial | Yes | Research articles, manufacturers' product data sheets, safety monitoring databases | Ethical F0006, Description and technical characteristics B0012, B0014, B0015 | | |
| C0063 | Safety risk management | How can one reduce safety risks for professionals (includingtechnology-, user-, and patient-dependent aspects)? | Is there a requirement for specific training, use of a protocol or available guideline which may reduce the occurrence or severity of the harm.<br><br>Information on what kind of risk communication is needed for patients, citizens and decision makers may be included. | Important | Partial | Yes | Research in occupational health and safety research literature | Organisational and Social Domains | | |
| C0064 | Safety risk management | How can one reduce safety risks for environment (includingtechnology-, user-, and patient- | Is there a requirement for specific training, use of a protocol or available guideline which may reduce the occurrence or severity of the harm.<br><br>Information on what kind of risk communication is needed | Important | Partial | Yes | Research articles, manufacturers' product data sheets. | Social Domain | | |

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| | | dependent aspects) | for patients, citizens and decision makers may be included. | | | | | | | |
| B0010 | Safety risk management | What kind of data/records and/or registry is needed to monitor the use of the technology and the comparator? | Describe the data that needs to be collected about the care process, professionals involved, patients and their health outcomes. These include: e.g. clinical indications, specified populations, prescriber information, inpatient or outpatient use, test results, review period, and health outcomes. In case of new technologies, consult EVIDENT database.<br><br>Describe the general importance of having a registry to monitor the use of this particular technology and the comparator. Are there existing registries that should be used, or should a registry be established, to collect the necessary data to monitor safety or true life effectiveness? Provide national examples.<br><br>Refer to SPC and EPAR.<br><br>Sometimes registries are connected with the risk sharing scheme that | Critical | Partial | Yes | Sources: Local authorities and legislation, administrative staff, clinical professionals, HTAs, National or local judgement. | G0008<br><br>G0003 | | Liberati A. et al. 1997; Busse R. et al. 2002; Kristensen FB et al. 2001; Draborg E et al. 2005 |

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| | | | innovative pharmaceuticals require in some countries. Notice also the requirements of pharmacovigilance monitoring. | | | | | | | |

## 4 Clinical Effectiveness

| ID | Topic | Issue | Clarification | Import. | Transf. | Is core | Methodology | Content relations | Sequential relations | References |
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| D0001 | Mortality | What is the expected beneficial effect of the technology on mortality? | Mortality is the preferred, objective endpoint for assessments of life-threatening conditions. Overall mortality and disease-specific mortality are distinguished. Overall mortality refers to all-cause mortality. It is expressed either as mortality rates (incidence in given population, at given time point and usually risk standardised), or survival (number of people alive for a given period after an intervention). Disease-specific mortality is a proportion of the all-cause mortality. It should be noted that even if a given treatment reduces one type of death, it could increase the risk of dying from another cause, to an equal or greater extent. Disease-specific mortality is typically presented as rates and asage- and risk- adjusted measures such as hazard ratio. It is a frequently used endpoint in screening trials, where it is considered to be subject to bias. | Critical | Complete | Yes | Systematic reviews of trials, trials, both placebo-controlled and with active control. In the absence of head to head trials, studies with indirect comparison (see Methodological guideline for REA of pharmaceuticals: Direct and indirect comparison, http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Direct%20and%20indirect%20comparisons.pdf). If these are not available, non-controlled studies and | E0005<br><br>F0001 | | Hochman 2011, Black 2002 |

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| | | | Several methods are used to adjust mortality rates and survival curves, e.g. relative survival (observed versus expected survival), which can be quite misleading; and hazard ratio (derived from a statistical method comparing the median survivals in the two groups). Note that progression-free survival is not a mortality endpoint; it describes the time from the beginning of an intervention until a patient shows signs of disease progression.<br><br>Consider separately absolute mortality (compared to placebo or waiting list) and mortality relative to the comparator. See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf<br><br>Supplement with relevant data if differences can be expected for specific subgroups. | | | | respective systematic reviews. Health care register data. Modelling studies.<br><br>Submission file, SPC, EPARs, | | | |

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| | | | See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf | | | | | | | |
| D0003 | Mortality | What is the effect of the technology on the mortality due to causes other than the target disease? | This issue includes all unintended, either positive or negative effects of the technology on mortality. There may be e.g. decrease of mortality of another disease observed or suspected; or increased mortality due to accidents or hazardous medical interventions after false positive or incidental test results.<br><br>Supplement with relevant data if differences can be expected for specific subgroups. | Important | Partial | Yes | Systematic reviews of trials, trials, both placebo-controlled and with active control. In the absence of head to head trials, studies with indirect comparison (see Methodological guideline for REA of pharmaceuticals: Direct and indirect comparison, http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Direct%20and%20indirect% | C0008<br><br>E0005<br><br>C0005 | | |

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| | | | | | | | 20comparisons .pdf). If these are not available, non-controlled studies and respective systematic reviews. Health care register data. Modelling studies.<br><br>Submission file, SPC, EPARs, | | | |
| D0005 | Morbidity | How does the technology affect symptoms and findings (severity, frequency) of the disease or health condition? | Describe the efficacy and effectiveness of the technology on relevant disease outcomes and other changes in physical and psychological conditions. Outcomes such as function, quality of life and patient satisfaction are reported in other assessment elements of this domain. Report changes in severity, frequency and recurrence of symptoms and findings, both in absolute terms and relative to the comparator.<br><br>Supplement with relevant data if differences can be expected for specific | Critical | Partial | Yes | Trials, observational studies<br><br>,,SPC and EPAR. | H0005<br><br>E0005 | | |

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| | | | subgroups.<br><br>See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf | | | | | | | |
| D0006 | Morbidity | How does the technology affect progression (or recurrence) of the disease or health condition? | Report here outcomes such as complete cure, progression-free survival, time-to-event (next stage of disease, relapse). Describe here the duration of treatment effect on symptoms and findings: permanent, short term, long term, intermittent, undulating. Report the results both in absolute terms and relative to the comparator. See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf<br><br>Supplement with relevant | Critical | Partial | Yes | Trials, prognostic studies<br><br>, SPC and EPAR. | E0005 | | |

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| | | | data if differences can be expected for specific subgroups. | | | | | | | |
| D0010 | Change-in management | How does the technology modify the need for hospitalization? | Consider also changes at different levels of care e.g. ward instead of intensive care. | Important | Partial | Yes | Trials, observational studies | E0001<br><br>G0001 | | |
| D0023 | Change-in management | How does the technology modify the need for other technologies and use of resources? | New (less invasive) interventions can reduce the need for surgical interventions. Some treatments require ongoing monitoring and healthcare visits including hospitalisation. | Important | Partial | Yes | Trials and pharmaco-economic studies, guidelines on utilization of resources. Observational studies, statistics | B0013<br><br>E0001<br><br>F0003<br><br>G0001, G0003, G0004, G0007 | G0001,G0003,G0007 | |
| D0011 | Function | What is the effect of the technology on patients' body functions? | International classification of function proposes the following categories for body functions: mental, sensory and pain, voice and speech, cardiac, respiratory and immune functions, genitourinary and reproductive functions, movement-related, and skin functions. Report the results both in absolute terms and | Critical | Partial | Yes | Trials and observational studies with functioning as an outcome. The instruments for outcome reporting should be validated<br><br>SPC and | H0005<br><br>E0005<br><br>F0101 | | ICF http://apps.who.int/classifications/icfbrowser |

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| | | | relative to the comparator.<br><br>Supplement with relevant data if differences can be expected for specific subgroups.<br><br>See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf | | | | EPAR.. | | | |
| D0014 | Function | What is the effect of the technology on work ability? | Describe the effects of the intervention on sick leave, absenteism, presenteism, return-to-work, retirement and other relevant outcomes describing working ability | Critical | Partial | Yes | Trials and other studies with return-to-work or work ability outcomes reported. | H0005<br><br>E0001 | | Fit for Work Europe website. Available at: www.fitforworkeurope.eu<br><br>European Commission (2007). Together for Health: A Strategic Approach for the EU 2008-2013. Available at http://ec.europa.eu/health-eu/doc/whitepaper_en.pdf |
| D0015 | Function | What is the effect of the technology on return to | Discharge to the living conditions in which patients lived before admission is one | Critical | Partial | Yes | Trials and observational studies using | H0005 | | |

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| | | previous living conditions? | of the most important treatment goals particularly for elderly patients. Implications for family members and carers should be considered too. | | | | one of the several evaluation tools, such as the Katz ADL scale, the Lawton IADL scale or the Bristol Activities of Daily Living Scale.<br><br>Health care service providers may use ADL evaluations in their practice, using models such as the Roper-Logan-Tierney model of nursing, and the resident-centered models, such as the Program of All-Inclusive Care for the Elderly (PACE). | | | |
| D0016 | Function | How does the use of the technology affect | Activities of Daily Living (ADL) is used in rehabilitation as an umbrella term relating to self care, comprising those | Critical | Partial | Yes | Trials and observational studiesreportin g ADL | H0005 | | |

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| | | activities of daily living? | activities or tasks that people undertake routinely in their every day life. The activities can be subdivided into personal care and domestic and community activities. Report the results both in absolute terms and relative to the comparator. For further information see guideline Health-related quality of life and utility measures http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf, and guideline: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf<br><br>Supplement with relevant data if differences can be expected for specific subgroups. | | | | outcomes<br><br>, SPC and EPAR | | | |
| D0012 | Health-related Quality of life | What is the effect of the technology on generic health-related quality of life? | Health related quality of life (HRQL) is typically measured with self- or interviewer-administered questionnaires to measure cross-sectional differences in quality of life between patients at a point in | Critical | Complete | Yes | Trials, observational and qualitative studies<br><br>, SPC and | H0005<br><br>E0005 | | EMEA 2005, FDA 2009, Chassany 2002, Terwee 2007, Revicki 2008, Puhan 2006 |

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| | | | time (discriminative instruments) or longitudinal changes in HRQL within patients during a period of time (evaluative instruments). Two basic approaches to quality-of-life measurement are available: generic instruments that provide a summary of HRQL; and specific instruments that focus on problems associated with single disease states, patient groups, or areas of function. Generic instruments include health profiles and instruments that generate health utilities. Each approach has its strengths and weaknesses and may be suitable for different circumstances. See also •Methodological guideline for REA of pharmaceuticals: Health-related quality of life and utility measures. http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf<br><br>Supplement with relevant data if differences can be expected for specific subgroups. | | | | EPAR. | | | |

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| D0013 | Health-related Quality of life | What is the effect of the technology on disease-specific quality of life? | Health related quality of life (HRQL) is typically measured with self- or interviewer-administered questionnaires to measure cross-sectional differences in quality of life between patients at a point in time (discriminative instruments) or longitudinal changes in HRQL within patients during a period of time (evaluative instruments). Two basic approaches to quality-of-life measurement are available: generic instruments that provide a summary of HRQL; and specific instruments that focus on problems associated with single disease states, patient groups, or areas of function. Each approach has its strengths and weaknesses and may be suitable for different circumstances.See also •Methodological guideline for REA of pharmaceuticals: Health-related quality of life. http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Health-related%20quality%20of%20life.pdf<br><br>Supplement with relevant | Critical | Partial | Yes | Trials, observational and qualitative studies<br><br>SPC and EPAR. | H0005<br><br>E0005 | | EMEA 2005, FDA 2009, Chassany 2002, Terwee 2007, Revicki 2008, Puhan 2006 |

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| | | | data if differences can be expected for specific subgroups. | | | | | | | |
| D0017 | Patient satisfaction | Was the use of the technology worthwhile? | Describe patients' overall perception of the value of the intervention and their satisfaction with the treatment. See also Methodological guideline for REA of pharmaceuticals: Endpoints used for relative effectiveness assessment of pharmaceuticals, clinical endpoints http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Clinical%20endpoints.pdf | Optional | None | No | Surveys, qualitative research, observational studies, trials | H0006<br><br>F0001, F0011 | H0006 | |
| D0029 | Benefit-harm balance | What are the overall benefits and harms of the technology in health outcomes? | This question integrates all benefits and harms concerning mortality, morbidity, QoL and further patient relevant outcomes, also considering the amount of false positive and false negative test results. There is no common quantitative summary measure, and even qualitatively a balanced and meaningful presentation is difficult to reach.<br><br>The integration of information across domains into the benefit-harm-balance is | Critical | Partial | Yes | Trials, observational studies, modelling studies | A0007, A0011, C0008, C0003, C0004, C0005, C0006, C0007, C0061, E0005, F0001, F0011 | A0007, A0011, C0008, C0003, C0004, C0005, C0006, C0007, C0061, | |

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| | | | essential. This issue provides input for ETH (F0010) andECO (E0005) to calculate the incremental effectiveness of the new technology. Information from SAF is needed for this issue: all harms to the patient are listed in outcomes and units which are comparable to the outcomes in EFF domain representing benefits.<br><br>See Template 7 in the the HTA Core Model for Rapid Relative Effectiveness Assessment of pharmaceuticals http://www.eunethta.eu/sites/5026.fedimbo.belgium.be/files/Model%20for%20Rapid%20REA%20of%20pharmaceuticals_final_20130311_reduced.pdf | | | | | | | |

## 5 Costs and economic evaluation

| ID | Topic | Issue | Clarification | Import. | Transf. | Is core | Methodology | Content relations | Sequential relations | References |
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| E0001 | Resource utilization | What types of resources are used when delivering the assessed technology and its comparators (resource-use identification)? | Report the resource items taken into account for each technology, as well as the sources of information used when identifying these and the reasons for their inclusion. Providing the results in tabular form is recommended. | Critical | Partial | Yes | Health-care registers and databases, RCT's with resource utilization data, reimbursement databases, micro-level costing studies/ABC-costing studies. Data may be available from different registers, and sources e.g., on sick leave, sickness allowance, patient administration systems/ clinical databases, earlier studies, cost diaries. | A0011, A0017, A0024, A0025<br><br>B0007, B0008, B0009<br><br>D0010, D0014, D0023<br><br>F0012<br><br>G0001, G0003, G0004, G0005, G0006, G0007<br><br>H0003, H0010 | A0017, A0024, A0025<br><br>B0007, B0008, B0009<br><br>D0010, D0023<br><br>G0001 | Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}. |
| E0002 | Resource utilization | What amounts of resources | Report the parameters required to estimate overall | Critical | Partial | Yes | Health-care registers and | E0001 | E0001 | Gold et al. {59}; Drummond et al. {1}; |

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| | | are used when delivering the assessed technology and its comparators (resource-use measurement)? | costs (E0009). Include the appropriate values, ranges, probability distributions as well as all references used. Providing the results in tabular form is recommended.<br><br>Report the approach(es) and data source(s) used to measure resource use associated with the technologies. | | | | databases, RCT's with resource utilization data, reimbursement databases, micro-level costing studies/ABC-costing studies | | | CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}. |
| E0009 | Resource utilization | What were the measured and/or estimated costs of the assessed technology and its comparator(s) (resource-use valuation)? | For each technology report mean values of estimated costs and, where possible, information concerning distributions surrounding these estimates. Cost estimates from different viewpoints can be reported here (e.g., patient, hospital, societal). In addition, reporting disease-stage-specific cost estimates and costs estimated using varied discount rates. Providing the results in tabular form is recommended.<br><br>Report the approach(es) and data source(s) used to estimate the costs associated with the technologies. | Critical | Partial | Yes | Market prices, companies, hospital accounting or reimbursement systems, as well as micro level costing studies/ABC-costing studies, or other information on unit cost s. | E0001, E0002 | E0001, E0002 | Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}. |

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| E0005 | Measurement and estimation of outcomes | What is(are) the measured and/or estimated health-related outcome(s) of the assessed technology and its comparator(s)? | For each technology report mean values of estimated effects and, where possible, information concerning distributions surrounding these estimates. It is suggested that estimates are expressed in natural units first, whenever possible, before using them in alternative forms such as QALYs.<br><br>Report the approach(es) and data source(s) used to estimate the outcomes associated with the technologies. | Critical | Partial | Yes | Estimation of the incremental or other effects can be based on information provided in the Clinical effectiveness domain (e.g., mortality data). Additional information collection may be needed (e.g. on health-related quality of life indices). The incremental effectiveness may result from an economic model, where inputs from the effectiveness domain are used. | A0004, A0005, A0006, A0009<br><br>C0008, C0002, C0004, C0006,<br><br>D0001, D0003, D0005, D0006, D0007, D0011, D0012, D0013,D0029<br><br>F0003, F0010, F0011<br><br>H0100 | A0004<br><br>C0008<br><br>D0001, D0005, D0006, D0007, D0012, D0029 | Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}.<br><br>Williams {60}; Johannesson et al. {61}. |
| E0006 | Examination of costs and outcomes | What are the estimated differences in costs and outcomes between the | For each technology report mean values of estimated costs and effects together. There are numerous ways of highlighting or comparing the differences in the costs and effects of the technologies | Critical | Partial | Yes | Relevant sources of data and evidence are specified in the relevant issues under the domains | E0001, E0002, E0005, E0009 | E0001, E0002, E0005, E0009 | Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et |

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| | | technology and its comparator(s)? | under assessment, typically, one or more of the following outcomes or approaches are used when reporting the results of health-economic evaluations:<br><br>- listing the cost and outcomes of each technology in tabular form<br><br>- an incremental cost-effectiveness ratio (ICER)<br><br>- an incremental cost effectiveness plane or efficiency frontier<br><br>- the net monetary benefit (NMB) and/or net health benefit (NHB)<br><br>Report the approach(es) and data source(s) used to estimate the of costs, outcomes, or economic evaluation(s) associated with the technologies. | | | | Safety , Clinical effectiveness and Costs and economic evaluation (bringing together the information collected in assessment elements E0009 and E0005). For example, ICER estimates from a de novo economic model could be reported, synthesising inputs from the Safety , Clinical effectiveness and Costs and economic evaluation domains. | | | al. {51}.<br><br>Briggs et al. {26}.; Glick et al. {29}; Johannesson et al. {61}. |
| E0010 | Characterising uncertainty | What are the uncertainties surrounding the costs and economic | The effects of uncertainty should be reported separately for parameter, structural and methodological uncertainty, whenever possible. For example: | Critical | Partial | Yes | Relevant sources of evidence are specified under relevant issues under domains Safety and | E0006 | E0006 | Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et |

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| | | evaluation(s) of the technology and its comparator(s)? | - deterministic sensitivity analysis in tabular form or using a Tornado diagram<br><br>- probabilistic sensitivity analysis, e.g., in the form of a CEAC<br><br>- value-of-information analysis<br><br>The methods used in the sensitivity analysis should be reported in detail here. | | | | Clinical effectiveness , as well as from within the Costs and economic evaluation domain. | | | al. {51}.<br><br>Bojke et al. {74}; NICE {69}; Briggs et al. {26}. |
| E0011 | Characterising heterogeneity | To what extent can differences in costs, outcomes, or 'cost effectiveness' be explained by variations between any subgroups using the technology and its comparator(s)? | If applicable, describe differences in costs, outcomes, or cost effectiveness that can be explained, e.g., by variations between (pre-defined) subgroups of patients with different baseline characteristics or other observed variability in effects. Providing the results in tabular form is recommended, but graphical representation using, e.g., 'Forest' plots may also be useful.<br><br>The methods used in any sub-group analysis should be reported in detail here. | Critical | Partial | Yes | Relevant sources of evidence are specified under relevant issues under domains Safety and Clinical effectiveness , as well as from within the Costs and economic evaluation domain. | C0005,<br><br>E0006<br><br>H0012 | E0006 | Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}.<br><br>Sculpher et al. {56}; Cleemput et al. {57} |

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| E0012 | Validity of the model(s) | To what extent can the estimates of costs, outcomes, or economic evaluation(s) be considered as providing valid descriptions of the technology and its comparator(s)? | It would be valuable to report any of the numerous ways of assessing to what extent the estimates for the technologies can be considered valid, For example:<br><br>- How well the model predicts health effects<br><br>- Whether model includes all aspects of resource use and costs considered important<br><br>- Estimates of the potential direction and/or potential magnitude of bias induced<br><br>- An attempt to identify key factors that could compromise the validity of the model<br><br>The process of validation and the types of validation addressed in the model should be reported here. | Critical | Partial | Yes | Relevant sources of evidence are specified under relevant issues under domains Safety and Clinical effectiveness , as well as from within the Costs and economic evaluation domain. | E0001, E0002, E0005, E0009, E0010, E0011 | E0001, E0002, E0005, E0009, E0010, E0011 | Gold et al. {59}; Drummond et al. {1}; CADTH {18}; Kristensen and Sigmund {3}; Cleemput et al. {57}; Husereau et al. {51}.<br><br>Eddy {38} |

## 6 Ethical analysis

| ID | Topic | Issue | Clarification | Import. | Transf. | Is core | Methodology | Content relations | Sequential relations | References |
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| A0005 | Beneficence/nonmaleficence | What are the symptoms and the burden of disease or health condition for the patient? | Describe the patient's relevant symptoms before intervention with the technology, their severity and whether they are persistent, intermittent, or undulating, taking into account different stages of the disease. Patients' perceptions of the burden of the disease are not always in line with the clinical seriousness of the disease or its societal burden.<br><br>This issue is especially relevant when the patient or individual is expected to undergo a substantial change in pain, disability, psychosocial issues, or other determinants of quality of life.<br><br>Knowing the severity level of the condition the technology is directed to is relevant in the ethical analysis of the technology. Information about the severity level is also important to decision-makers when making decisions about whether or not to implement | Critical | Complete | Yes | Sources: text books, HTAs, quality of life studies, qualitative patient perception studies.<br>Method: A descriptive summary. | | | Burls 2000 {1}, Busse 2002 {2}, Liberati 1997 {3}, Imaz-Iglesia 1999, Kristensen 2007 {24} |

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| | | | a technology. | | | | | | | |
| F0010 | Beneficence/nonmaleficence | What are the known and estimated benefits and harms for patients when implementing or not implementing the technology? | Decisions concerning implementation of new technologies generally require careful consideration of the balance between benefits and harms. Examples of questions that can be asked are:<br><br>Who is the right candidate for the technology? What is the balance between benefits and harms? For instance, is the technology estimated to improve health, health-related quality of life, quality of life and/or survival compared to alternative technologies? Can the technology harm individual patients, or any other stakeholder, in any way? How many patients might face harm in order for the technology to have a benefit for one patient? What is the extent of these benefits and harms?<br><br>What are the perceived benefits and harms of the technology in the eyes of the patients/users themselves? It might be useful to note that the patient is often the best | Critical | Partial | Yes | Information from other domains (links). Literature search. Expert opinion. Stakeholder hearing | | D0001,<br><br>D0029,<br><br>H0001, H0004, H0005,<br><br>H0006, C0008, C0005,<br><br>A0010<br><br>D0017 | 47 |

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| | | | judge of benefits and harms for themselves.<br><br>. | | | | | | | |
| F0011 | Beneficence/nonmaleficence | What are the benefits and harms of the technology for relatives, other patients, organisations, commercial entities, society, etc.? | Can the technology have positive effects for others than the patients in question? Can the technology harm relatives, other patient groups, organisations, commercial entities, society, etc.? Some technologies have the potential to unfold unwanted or harmful effects not only on the patients that the technology is directly applied to but also indirectly on others. For example results of genetic tests may negatively interfere with the family planning and social life of not only the individual being tested but also of his or her relatives. Another example is how the caregivers' burden and well-being will be affected by the technology.<br><br>Benefits and harms to individuals must be balanced with benefits and harms that can have impact on society as a whole (social utility, maximizing public health). These harmful effects may | Critical | Partial | Yes | Literature search. Expert opinion. Stakeholder hearing | | D0029,<br><br>H0001, H0002,<br><br>C0020, C0040,<br><br>A0006,<br><br>E0006,<br><br>D0017 | 1, 47 |

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| | | | manifest in the physical, social, financial or even other domains of life.<br><br>Changes in the availability of new, more effective technologies may significantly alter the requirements placed on the health care system. Is the symbolic value of the technology of any moral relevance?<br><br>Another relevant question is how the assessed technology relates to more general challenges of modern medicine (over-diagnosis, medicalization)?<br><br>Table 1 (link) in the process description can be used to describe benefits and harms. | | | | | | | |
| F0003 | Beneficence/nonmaleficence | Are there any other hidden or unintended consequences of the technology and its applications for patients/users, relatives, other | The technology may be used for other indications (extended use) or other purposes, e.g., in combination with other technologies (unintended use). It may have side-effects in addition to those following from the intended use. Ethical analysis of the technology should consider not only the consequences of | Critical | Partial | Yes | Literature search. Expert opinion. Stakeholder hearing | | | 49, 50 |

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| | | patients, organisations, commercial entities, society etc.? | the formal intended use of the technology, but also the ethical consequences of unintended and extended use. If unintended consequences are not well-known, they should be speculated and elaborated upon. The intended purpose and uses of the technology should be evaluated against the likely uses and consequences of the technology in reality.<br><br>The mode of delivery, the need of laboratory tests or clinical follow-up to ensure safe and effective dose, and way of delivery (at home, outpatient or in-patient) may have large impact on the health care processes, systems and on individuals. They may also change the concepts of disease and normality (e.g. change an untreatable cancer into a chronic disorder or changing the border values when the concept of normality also changes).<br><br>New technologies tend to lead to new areas of inventions and give rise to new ethical questions (e.g. IVF and development of | | | | | | | |

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| | | | genetic testing has led to questions of preimplantation genetic diagnostics (PGD)). As pre-symptomatic screening tests have become available, the health care system has to be prepared to handle moral issues raised by true positive and false negative findings.<br><br>The mode of delivery, the need of laboratory tests or clinical follow-up to ensure safe and effective dose, and way of delivery (at home, outpatient or in-patient) may have large impact on the health care processes, systems and on individuals. They may also change the concepts of disease and normality (e.g. change an untreatable cancer into a chronic disorder or changing the border values when the concept of normality also changes).<br><br>Another relevant question is whether or not there will be a moral obligation related to the implementation, withdrawal, or use of the technology (e.g. check-ups or alternative procedures).<br><br>Pharmaceuticals have | | | | | | | |

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| | | | usually been designed and studied for a specific and defined group of patients but they may be used for a larger group (variation in age and severity of the disorder and persons with comorbidities and/ or need of other pharmaceuticals). Expensive pharmaceuticals (orphan disorders, new cancer treatments) and prescribing pharmaceuticals according to genetic profiles challenges the equal and just use of health care resources. The health care system has to be prepared to handle moral issues raised by the new, expensive possibilities to treat rare, otherwise non-treatable disorders and to prolong life in chronic disorders. | | | | | | | |
| F0005 | Autonomy | Is the technology used for patients/people that are especially vulnerable? | The right and justification to use the technology for persons who are vulnerable has to be clarified. Persons that are vulnerable could for example be pregnant women as to protect their unborn child, critically ill patients or individuals that have reduced decision making capacity (children, persons with cognitive disabilities or | Critical | Complete | Yes | Literature search. Expert opinion. Stakeholder hearing | | C0005 | 52 |

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| | | | patients that due to their illness/state have limited decision making capacity). Who has the right to balance the benefit against possible harm in these situations? On what grounds can these decisions be made? Is the technology so valuable, as to justify its use on people who cannot give informed consent? | | | | | | | |
| F0004 | Autonomy | Does the implementation or use of the technology affect the patient´s capability and possibility to exercise autonomy? | Many technologies can alter a person´s self-determination. The technology may interfere with patients' right to autonomy directly or indirectly by influencing/subtracting the decisional capacity. However, patients have in most cases a right to autonomy, i.e. right to be self-governing agents. This means both the right to decide (not to) use/participate, and the right to receive relevant information. Drugs for sedation and surgical treatment of severely ill patients are examples where patient autonomy may be reduced.<br><br>Technology may require users/patients to behave in a | Critical | Partial | Yes | Literature search. Expert opinion. Stakeholder hearing | | H0013<br><br>D0012<br><br>D0013<br><br>D0016 | 49, 52 |

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| | | | certain way (e.g. dietary restrictions for fecal blood test). In order to be able to decide autonomously, the user/receiver of the technology should understand all alternative treatments or different therapeutic paths following test results. They should be able to make informed consent at every step.<br><br>The practical challenge with treatment technologies is that in order to be fully autonomous, the patient should understand not just direct risks of the treatment, but also all alternatives if side effects take place and how these can affect the living quality or choices (eg car driving, nutrition). | | | | | | | |
| F0006 | Autonomy | Is there a need for any specific interventions or supportive actions concerning information in order to respect patient autonomy | Is the common professional practice of discussing the technology with patients enough, or is special information needed to decide on this technology? Can the technology entail special challenges/risks that the patient/person needs to be informed of? Should the patient be explicitly informed, for example, that false | Critical | Complete | Yes | . Expert opinion. Stakeholder hearing | | H0013, H0007, H0008,<br><br>C0008, B0014,<br><br>I0002,<br><br>C0005 | 51 |

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| | | when the technology is used? | positive results of a test may lead to unnecessary further investigations and treatments, sometimes with serious harms. An example is screening programmes for early identification of life-threatening situations that may have life-threatening side effects such as invasive surgery with risk of death. Technology used for off-label use may have unexpected severe side-effects (e.g. patients with comorbidities or children).<br><br>The information should enable the user/receiver of the technology to understand the technology and its associated risks/challenges. It should be in accordance to their personal values and intellectual capacity, thereby enabling users to decide accordingly. The patient should be explicitly informed, for example, that the treatment may have serious side effects, may have an effect on personality or lead to increased need of sleep or overweight. They should also be informed of that the mode of delivery or action may affect their daily life (eg. no car driving allowed, restricted | | | | | | | |

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| | | | travelling). | | | | | | | |
| F0007 | Autonomy | Does the implementation or withdrawal of the technology challenge or change professional values, ethics or traditional roles? | Technologies may change the relationship between physician and patient, challenge professional autonomy or otherwise interfere with professional ethics and values. The patient-physician relationship is traditionally based on mutual trust, confidentiality and professional autonomy so that individual treatment decisions can be made in the best interest of the patient. Technologies that interfere with core values and principles of medical and professional ethics challenge the professional integrity of the physicians or other health care professionals (eg. screening for drug abuse when use is denied). Technologies that align with professional ethics are more likely to be implemented successfully. For example, people may ask for the technology for many reasons, while the professionals may see them as unnecessary and even potentially harmful (e.g. antibiotics, sleep medicine, antidepressants, | Critical | Partial | Yes | Expert opinion | | G0010 | 49, 53 |

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| | | | whole body MRI scans). | | | | | | | |
| F0008 | Respect for persons | Does the implementation or use of the technology affect human dignity? | Especially technologies that are applied for persons with reduced autonomy (children, mentally impaired, severely ill), may violate a person's dignity i.e. challenge the idea that all human beings have intrinsic value, and should thus not be seen as means to others ends. Labelling people as result of use of the technology may also threaten their dignity.<br><br>Some technologies may cause labelling healthy people as sick (eg PSA for prostate cancer) or otherwise less worthy, abnormal, less clean, etc. For instance labelling people as needing psychiatric medication for their behavioural difficulties may threaten their dignity. People with physical disabilities may be labelled by prenatal screening programmes, which imply that their handicap is an indication for abortion. | Critical | Partial | Yes | Literature search. Expert opinion. Stakeholder hearing | | | 49, 54 |
| F0009 | Respect for persons | Does the implementation or use of the | The technology can challenge integrity by preventing (or tempting to | Critical | Partial | Yes | Literature search. Expert opinion. | | H0011, H0013 | 49, 50 |

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| | | technology affect the user´s moral, religious or cultural integrity? | prevent) patients to live according to their moral convictions, values, preferences or commitments. It may also interfere with the coherent image or identity of the users´ selves. This is especially important to analyse for vulnerable patient groups.<br><br>The technology may challenge religious, cultural or moral convictions or beliefs of some groups (e.g. pharmaceuticals produced from human blood given to cultural groups that will not tolerate blood transfusion, pharmaceuticals used for abortion in cultural groups that will not tolerate abortion and assisted reproductive technologies that have separated the concept of genetic, biological and social motherhood).<br><br>The technology may change generally or locally accepted social arrangements by challenging traditional conceptions or social roles. For instance ADHD medication might challenge the integrity of people who value personality, and cochlear implants may be | | | | Stakeholder hearing | | | |

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| | | | problematic for those who do not see deafness as a disability.<br><br>Identifying the conceptions behind the beliefs and values may help put them in perspective, when considering the ethical consequences of use and the overall acceptability of the technology. When possible, considering other acceptable alternatives for the affected groups of users is important. Use of the technology can also be detrimental to integrity if it is associated with discouraging honesty or ethical conduct, e.g., systems that encourages users to lie about their health state in order to get better service/treatment. | | | | | | | |
| F0101 | Respect for persons | Does the technology invade the sphere of privacy of the patient/user ? | The sphere of privacy can be invaded both virtually and physically. Does the technology affect the population's possibility to have control over personal information? Is dissemination or gathering of information regarding the individual patient or the population justified? Is cooperation and sharing of information with | Critical | Partial | Yes | Literature search. Expert opinion. Stakeholder hearing | | B0010, D0011,<br><br>I0007, I0009,<br><br>I0002 | 51 |

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| | | | professional groups outside the health services needed? Is the handling of personal information reasonable given the purpose of using the technology? Is the technology more or less invasive than the alternatives, regarding the physical body and/or the spatial sphere? Is a violation of the privacy of the patient or population necessary and reasonable to achieve desired outcomes? | | | | | | | |
| F0012 | Justice and Equity | How does implementation or withdrawal of the technology affect the distribution of health care resources? | Many technologies imply substantial costs, sometimes covered with resources from other areas. A new technology may require reallocation of human resources, funding and training. A large reallocation of resources may seriously jeopardize other patient groups (e.g. new technology that requires human resources in acute care or new diagnostic technology that uncovers a large pool of unmet needs for treatment). How this reallocation affects the existing health care system has to be studied. Who will gain and who will lose? Is the prioritization | Critical | Partial | Yes | Expert opinion. | | G0007,<br><br>E0001,E0002, E0009 | 49, 55, 56 |

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| | | | explicit or implicit?<br><br>Pharmaceuticals may acquire abstract promise of health benefit that may create demand that is not justified. Some diagnosis may create demands for pharmaceuticals that are not always justified to be prescribed on health grounds (eg. large variation in prescribing ADHD medication for children by various countries). | | | | | | | |
| F0013 | Justice and Equity | How are technologies with similar ethical issues treated in the health care system? | Clearly presenting how technologies with similar ethical issues are treated in a health care system may help to adopt coherent and just health policies, either by applying past precedents to current cases, or showing that past cases need reconsideration. Similarity is to be defined individually for each technology. The idea is to concentrate only on the similarities relevant for solving the ethical problems found important for the current HTA project. The similar ethical problems can be related to similarities in the technology's medical, technological, economic, social, organisational or legal | Important | Partial | Yes | Literature search. Expert opinion | | | 49 |

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| | | | nature. | | | | | | | |
| H0012 | Justice and Equity | Are there factors that could prevent a group or person from gaining access to the technology? | Can the technology be applied in a way that gives equal access to those in equal need? How can this be guaranteed? Could potential discrimination or other inequalities (geographic, gender, ethnic, religious, and employment, insurance) prevent access? Potential inequalities and discrimination should be justified. Issues of access to a technology as well as labelling and potential discrimination of persons receiving and not receiving treatment should be considered.<br><br>Are special groups discriminated?. Ethical and social issues have often been considered in academic articles and discussions in the HTA field, but they have rarely been translated into practice. | Critical | Partial | Yes | Implement the best available evidence about social restrictions, social pressure, social attitudes | SHARED with SOC domain H0012<br><br>Legal domain | G0009, G0101<br><br>A0012<br><br>I0011 | See social domain |
| F0014 | Legislation | Does the implementation or use of the technology affect the | The basic human rights are most notably declared in the United Nations Declaration of Human Rights (Ref: http://www.un.org/en/docume | Critical | Complete | Yes | Literature search. Law, rules and regulations. Expert opinion. | SHARED between ethical and legal | H0012 | 49, 57 |

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| | | realisation of basic human rights? | nts/udhr/). They are universal and consider the most important goods, protections and freedoms for mankind. For HTA, perhaps the most relevant are the rights to equality, non-discrimination, safety, adequate standard of living and health care. | | | | Stakeholder hearing | domains | | |
| F0016 | Legislation | Can the use of the technology pose ethical challenges that have not been considered in the existing legislations and regulations ? | Is legislation and regulation to use the technology fair and adequate? Use of the technology may lead to ethical issues that make current regulations inadequate. Screening and diagnostic technologies are commonly differently regulated than treatments, especially medications. Ethical reflection is essential in order to assess what kind of legislation, regulation or amendments is needed (see also legal domain). | Important | None | No | Law, rules and regulations. Stakeholder hearing. Expert opinion | SHARED between ethical and legal domains | B0010, I0011,<br>I0009,<br>I0002,<br>I0026<br>I0037 | 49, 58 |
| F0017 | Ethical consequences of the HTA | What are the ethical consequences of the choice of end-points, cut-off values and comparators/controls in | Is there a risk that the chosen end points, cut-off values or comparators/controls may give a biased description of the results of the technology?<br><br>Clinical effectiveness should ideally be directly related to the disease under treatment. | Critical | Partial | Yes | Other domains:, safety, effectiveness. Expert opinion, Stakeholder hearing | | See methodological description in EFF and SAF | 49 |

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| | | the assessment ? | This is not always fully possible so other endpoints may have to be used (e.g. surrogate markers for preventing a life-threatening disease). In addition, the technology may have several aims (e.g. those related to treating the disease and preventing secondary morbidity).<br><br>The choice of cut-off values for sensitivity and specificity should be done considering the moral value of different results – for example, high specificity is required if false positives have serious consequences. | | | | | | | |
| F0102 | Ethical consequences of the HTA | Does the economic evaluation of the technology contain any ethical problems? | It is important to consider whether there are any ethical problems related to the data or assumptions that have been used in the economic valuation. An example is whether or not indirect costs have been valued in a fair and adequate way. | Important | Partial | Yes | Literature search, Expert opinion | | See methodological description in ECO | 9, 51 |
| F0103 | Ethical consequences of the HTA | What are the ethical consequences of the assessment of the | At what time of the lifetime of the technology is it assessed? Who will (not) get access to the new technology, as a result of the | Important | Partial | Yes | Expert opinion, Stakeholder hearing | | | 49 |

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| | | technology? | conclusions of the HTA? What are the consequences of assessing the technology with respect to prioritisation? | | | | | | | |

## 7 Organisational aspects

| ID | Topic | Issue | Clarification | Import. | Transf. | Is core | Methodology | Content relations | Sequential relations | References |
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| G0001 | Health delivery process | How does the technology affect the current work processes? | Current tasks and work processes should be described. This help to make a picture of the whole process as well as the continuity of care across professional and organisational boundaries. Who is doing what in the process?<br><br>There are many actors at different levels (intra-organisational, inter-organisational and health care system level) in the process. Continuity should be ensured so that there will be no gaps between the steps of the process.<br><br>It should be explained what kind of changes a new technology could have: it might replace or reduce some activities.<br><br>This issue is about patient path way by the point of view of patient/participant. Patient path should be described step by step. This includes | Critical | Partial | Yes | Literature search, guidelines, annual reports and statistics, reports and own study (e.g. questionnaires and interviews of different actors)<br><br>Literature search, guidelines, annual reports and statistics, reports and own study (e.g. questionnaires and interviews of different actors) | : A0013, A0014,A0024, B0004, C0063, D0020, D0021, D0023, F0001, F0007, I0002, I0009 | A0007, A0023, A0011<br><br>Order of doing; to be answered prior to: E0001 | {1, 14}<br><br>{1, 14} |

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| | | | also the waiting times for diagnosis and/or treatment and waiting time for analysis of the technology.<br><br>Preparations that patients/participants need to do before and after (e.g. diet before bariatric surgery) must be taken into account, as well as need for self/home monitoring.<br><br>The differences of the work processes between the new medicine and the comparator have to be specified. For example new medicine does not need routine laboratory unlike the comparator. | | | | | | | |
| G0100 | Health delivery process | What kind of patient/participant flow is associated with the new technology? | This issue is about patient path way by the point of view of patient/participant. Patient path should be described step by step. This includes also the waiting times for diagnosis and/or treatment and waiting time for analysis of the technology.<br><br>Preparations that patients/participants need to do before and after (e.g. diet before bariatric surgery) must be taken into account, as well as need for self/home | Critical | Partial | Yes | Literature search, guidelines, annual reports and statistics, reports and own study (e.g. questionnaires and interviews of different actors) | | A0010, H0003<br><br>Order of doing; to be answered prior to: E0001 | {1, 14} |

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| | | | monitoring. | | | | | | | |
| G0002 | Health delivery process | What kind of involvement has to be mobilized for patients/participants and important others? | This issue is about the role of patients/participants. A new technology may require distribution of tasks among the people involved in the treatment and care. Patients/participants and their important others may be more actively involved in own care and treatment – or tasks they used to carry out may be taken over by health professionals.<br><br>The way patient get the medicine and how he is involved in the follow-up (monitoring by patients/participants or by their important others). | Important | Partial | Yes | Literature search, annual reports and statistics reports, hospital documents and own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory, participants). | B0014, H0003, H0010, H0006, H0007, H0008, H0009, H0013 | A0007 Order of doing; to be answered prior to: H0002 | {14} |
| G0003 | Health delivery process | What is the process ensuring proper education and training of the staff? | New technology may require new kind of professionals or new tasks for existing personnel. This issue is about how the organisation can manage to ensure proper education. It had to take into account how training affects the management and effectiveness.<br><br>Implementing a technology can change the job and thus | Important | Partial | Yes | Literature search, guidelines, reports and documents of the hospital or hospital districts and own study: interview or questionnaires of different actors of the | A0013, A0014, B0012, C0063, D0023, E0001, E0002, F0007, legal? | B0013<br><br>Order of doing; to be answered prior to: E0003 | {1, 14, 26} |

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| | | | have influence on job satisfaction. | | | | process. | | | |
| G0004 | Health delivery process | What kind of co-operation and communication of activities have to be mobilised? | Co-operation and communication is crucial for fluent patient pathway. Implementing a technology can demand new co-operation and communication in- and outside the organization, e.g. other hospitals, pharmacies and manufactures. Therefore structure of co-ordination is important. Also, interaction and communication with patients/participants and their important others could change. Adaptation of self/home monitoring needs close co-operation and fluent communication. | Critical | Partial | Yes | Literature search, guidelines, reports and documents of hospital and hospital districts, guidelines, own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory, participants). | B0014, B0015, C0063, D0023,H0010, H0007, H0008, H0009, H0013, I0002 | | {1, 14} {27} |
| G0012 | Health delivery process | How is the quality assurance and monitoring system of the new technology organised? | A new technology usually have an effect on current quality assurance not only inside the organization but also outside in different health care levels. To assure the quality, a monitoring system with standards and indicators are needed. There could be variations how | Important | Partial | Yes | Literature search, annual reports and statistics reports of hospitals and own study: questionnaires and interviews of different | B0010, B0012, B0020, C0007, E0001, E0002, | B0020<br><br>Order of doing: to be answered prior to E0003 | {14} |

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| | | | quality assurance and monitoring system has been implemented. It had to be taken into account who is responsible for quality assurance and for monitoring system and how follow up has been arranged.<br><br>It had to take into account how quality assurance and monitoring system affects the management and effectiveness.<br><br>There could be international, national, regional and/or (cross) organisational demands for quality assurance (e.g. quality standards and monitoring) and for registration.<br><br>What information have to be gathered (clinical indicators, special patient groups, laboratory results)?<br><br>There are national standards for Pharmacovigilance of pharmaceuticals. Some countries legally oblige physicians to report the adverse events. In most countries, manufacturers are required to submit all the reports of adverse events they receive from healthcare | | | | actors of the process (monitoring authorities, hospitals, hospital districts, laboratories). Information from manufacturers.<br>. | | | |

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| | | | providers to the national authority. A specific monitoring system is may be necessary for innovative pharmaceuticals. | | | | | | | |
| G0005 | Structure of health care system | How does de-centralisation or centralization requirements influence the implementation of the technology? | The setting (primary - secondary - tertiary care) can vary between different countries depending on the health care system. (De)centralisation could have some economical and qualitative benefits. Centralisation could make the technology more difficult to access. Usually, expensive technologies are centralised to tertiary care units with special educated staff.<br><br>In what health care level the medicine is implemented? | Important | Partial | Yes | Literature search, guidelines, reports and documents of hospital and hospital districts, health information databases (DRG etc.), own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory, participants).<br><br>Literature search, guidelines, reports and documents of hospital and | | B0004, F0012 | {1, 14, 26, 27} |

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| | | | | | | | hospital districts, health information databases (DRG etc.), own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory, participants). | | | |
| G0101 | Structure of health care system | What are the processes ensuring access to care of the new technology for patients/participants? | Access to care is often measured in terms of utilisation. There are different viewpoints: individual, population-specific and health system factors. Access to care is related to e.g. social, cultural, economic, organisational, relational or geographical factors.<br><br>Access to care by wide definition includes availability, accessibility, accommodation, affordability and acceptability. | Critical | Partial | Yes | Literature search, guidelines, reports and documents of hospital and hospital districts, health information databases (DRG etc.), own study: questionnaires and interviews of different actors of the process (monitoring | | A0001, H0012 | |

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| | | | This issue is related to the issue of acceptability of new technology (G0010) | | | | authorities, hospitals, hospital districts, laboratory, participants). | | | |
| G0006 | Process-related costs | What are the processes related to purchasing and setting up the new technology? | Implementing the required changes in e.g. premises may be costly for organisations. High costs can influence the decision to introduce the new technology. There may be division of costs such that some organisation(s) is(are) responsible for the acquisition costs and others for the running costs. Investments by, at all stages of the process, should be taken into consideration.<br><br>This includes e.g. devices, special room and software needed for the new medicine. | Critical | Partial | Yes | Literature search, guidelines, reports and documents of hospitals and hospital districts and manufacturers (e.g. producer handbook), own study: questionnaires and interviews of different actors of the screening process (monitoring authorities, hospitals, hospital districts, laboratory | | B0007, B0008, B0009,<br><br>Order of doing: to be answered prior to E0001 | {14} |
| G0007 | Process-related costs | What are the likely budget impacts of implementin | Whenever a technology is introduced, there will be an impact on health care budgets. Budget impact | Critical | None | Yes | Literature search, reports questionnaires and interviews | A0011, A0020, B0007, B0009,D0 | Order of doing; to be answered prior | {14, 28} |

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| | | g the technologies being compared? | analysis attemps to examine the likely impact of introducing a technology on financial outlays from, e.g., the perspective of different payers. Different payers include: government-level insittutions; regions; municipalities; employers; insurance companies and patients/participants. The relevant perspective from which to estimate budget impact may change during different phases of the management process and incentives are connected to this issue. For example: What kind of incentives does the budget impact impose on different actors? How might this potentially impact on each organization? What is the estimated net financial (e.g. annual) cost of introducing the technology? Budget impact analysis provides data to inform an assessment of the affordability of a technology. It also provides a service planning tool to inform decisions about taking the technology into use. | | | | of different actors of the screening process (monitoring authorities, hospitals, hospital districts, laboratory), information from manufacturers. | 023, | to:E0001 | |
| G0008 | Management | What management problems | The issue concerns the administrative / managerial | Critical | Partial | Yes | Literature search, | A0011, A0012, | | {28} {29}{14} |

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| | | and opportunities are attached to the technology? | questions of technology: management of resources (e.g. investments), co-ordination (in relation to different levels and different steps of the process), establishment of objectives, monitoring and control (how quality assurance affects management or effectiveness), evaluation and sanctioning. Data/information management systems connected to each of these points have to take account.<br><br>This issue includes also risk management and safety issues (e.g. safety of personnel). | | | | guidelines, reports and documents of hospitals, own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital districts, laboratory). | A0015, A0016, A0017, A0025, B0020, C0063, D0021, H0009, I0009 | | |
| G0009 | Management | Who decides which people are eligible for the technology and on what basis? | Provide information on who are the key actors in deciding on the use of the technology. Do most important decisions take place on the national level (e.g. population screening) or for example by individual professionals (e.g. surgical method for a specific disease)? How is the decision made; are there some documented criteria?<br><br>Information about the possible variations in the | Important | Partial | Yes | Literature search, guidelines, documents of hospitals, own study: questionnaires and interviews of different actors of the process (monitoring authorities, hospitals, hospital | A0011<br><br>A0012<br><br>:B0016, D0021, F0012, I0012, H0012 | | Kristensen 2007 {24}<br><br>{14} |

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| | | | decision level and criteria has ethical implications.<br><br>This issue is related to the issue of work processes (G0001)<br><br>Companion diagnostics (tests or measurements) assist physicians in making treatment decisions for their patients by elucidating the efficacy and/or safety of a specific pharmaceutical or class of pharmaceuticals for a targeted patient group or sub-groups. How companion diagnotic should be used to identify eligible patient should be specified and explained.<br><br>Criteria must be specified for higher risk groups of patients such as elderly and children. | | | | districts, laboratory). | | | |
| G0010 | Culture | How is the technology accepted? | Acceptance should be looked at by different perspectives: by organisation, by personnel and by patients/participants. Organisational view can be separated out intra-organisational (primary care), inter-organisational (secondary care) and health care system level. In all these actors/views acceptance could vary. Alternative ways | Critical | Partial | Yes | Literature search, own study: questionnaires and interviews of different actors of the screening process (monitoring authorities, hospitals, | F0001, F0003, F0007, H0006, H0007, H0011,H0012 | | {14} |

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| | | | to introduce a new technology into the organisation could influence problems e.g. resistance among staff and dysfunction of processes.<br><br>Acceptability is related to access to care. | | | | hospital districts, screening units, laboratory, staff, participants). | | | |
| G0011 | Culture | How are the other interest groups taken into account in the planning / implementation of the technology? | It may be useful to know who are the possible stakeholders, as well as what kind of co-operation exists and what kind of interaction is needed. The stakeholders could be e.g. the pharmaceutical industry and companies offering technologies for screening, authorities (national / regional), registry, administrative parties, municipalities, policy makers / decision makers, staff groups, GPs/primary care physicians and patient organisation. One can also ask: Has the patient organisation taken part into the evaluation process? Has it been involved from the beginning (in the planning) or in the later stages for example as commentator? | Important | None | No | Literature search, reports and documents of hospitals, own study: questionnaires and interviews of different actors of the screening process (monitoring authorities, hospitals, hospital districts, screening units, laboratory, manufacturers, registry, participants). | A0022, B0015, F0003, F0011, | | {1, 14, 27} |

## 8 Social aspects

| ID | Topic | Issue | Clarification | Import. | Transf. | Is core | Methodology | Content relations | Sequential relations | References |
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| H0100 | Individual | What kind of changes do patients or citizens expect? | What do the patients expect to get out of the intervention before, during and after the intervention? Are there temporary changes that should be explained? | Critical | Partial | Yes | | ETH | | |
| H0002 | Individual | Who are the important others that may be affected, in addition to the individual using the technology? | Describe who are the important other people that are involved in the use of technology in addition to the patients (parents, children, friends, people at work place etc) | Critical | Partial | Yes | | ETH and LEG | | |
| H0003 | Individual | What kind of support and resources are needed for the patient or citizen as the technology is introduced? | This issue is about any kind of support and resources (practical, physical, emotional, personal social, nurturing, financial etc.) that need to be mobilized, and organized - or might be released - in order for the patient to use the technology with satisfactory results. It covers all arrangements or adjustments that may be needed (e.g. alteration of | Critical | Partial | Yes | | ORG | | (35): environmental factors: support and relationships (chapter 3: e310-399); " activities and participation, chapter 6: d698, structural arrangements of patient's environment. (17, 15, 14) |

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| | | | special tasks, working time, adjustments in the physical environment, emotional support). | | | | | | | |
| H0004 | Individual | What kind of changes may the use of the technology generate in the individual's role in the major life areas? | This issue is about the patient's social roles and ability to manage and maintain relations with other people in a socially appropriate manner in major life areas. | Critical | Partial | Yes | | ETH and SAF | | (35): activities and participation, interpersonal interactions and relationships (chapter 7, d710-779), community, social and civic life (chapter 9:d910-d999). (5, 7, 35, 36) |
| H0006 | Individual | How do patients, citizens and the important others using the technology react and act upon the technology? | This issue is about the patients and her important others' attitudes, perceptions, preferences, satisfaction and relations to the technology. This covers whether, from a patient perspective, any positive or negative issues arise as a consequence of using the technology e.g. feelings of unity or empowerment and existential experiences (e.g. insecurity, worries, hope, anxiety, stigmatisation, social status, courage to face life, satisfaction, changes in self-conception). | Critical | Partial | Yes | | EFF | | (35): body functions: mental functions (chapter 1:b110-b199), environmental factors: attitudes (chapter 4:, e410-499), (3) |

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| H0012 | Individual | Are there factors that could prevent a group or person from gaining access to the technology? | Can the technology be applied in a way that gives equal access to those in equal need? How can this be guaranteed? Could potential discrimination or other inequalities (geographic, gender, ethnic, religious, and employment, insurance) prevent access? Potential inequalities and discrimination should be justified. Issues of access to a technology as well as labelling and potential discrimination of persons receiving and not receiving treatment should be considered.<br><br>Are special groups discriminated?. Ethical and social issues have often been considered in academic articles and discussions in the HTA field, but they have rarely been translated into practice. | Critical | Partial | Yes | Implement the best available evidence about social restrictions, social pressure, social attitudes | SHARED with SOC domain H0012<br><br>Legal domain | G0009, G0101<br><br>A0012<br><br>I0011 | See social domain |
| H0011 | Major life areas | What kinds of reactions and consequences can the introduction of the technology | This issue is about the broader society. What social reactions can be expected for example from religious groups, specific patients and citizens organisations and associations and from any | Critical | Partial | Yes | Search for existing literature review, or collect primary studies and if possible | Ethical, organizational and Legal domains | | |

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| | | cause at the overall societal level? | other stakeholder groups (social burden with accepted versus stigmatising diseases)? Are special (social) risk groups defined (ethnic, age etc.) and their possible reactions assessed? | | | | conduct a litterateur review, or, if relevant data is not available, conduct a stakeholder analysis and a qualitative/quantitative primary study; if there's no time the systematic collection of opinion of some of the involved stakeholders and interest groups can be done. Patients, citizens and important others can be consulted. | | | |
| H0001 | Major life areas | Which social areas does the use of the technology influence? | Map the major life areas of the patient and the important others (family life, day care, school, work, leisure time, lifestyle, or other daily activities), where the technology is going to be used or where its use may have a direct or indirect | Critical | Partial | Yes | | | | |

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| | | | influence. | | | | | | | |
| H0009 | Major life areas | What influences patients' or citizens' decisions to use the technology? | What kind of societal influences lead patients to decide to participate? How do the provisional perceptions about the outcome influence the use of the technology | Critical | Partial | Yes | | ETH | | |
| H0007 | Information exchange | What is the knowledge and understanding of the technology in patients and citizens? | This issue explores the patient's and important others' understanding of the technology in order to describe and decide what guidance and help (e.g. patient information leaflets, counselling processes, need of follow up consultation or help from other professionals) they need before, during and after the use of the technology.<br><br>What kind of access do patients' and significant others' hav eto ask questions? How do they receive answers? How is information provided and received? | Critical | Partial | Yes | | CUR and SAF | | |
| H0013 | Information exchange | What are the social obstacles or prospects in | E.g. limitations to decision making in participating or using the technology | Critical | Partial | Yes | Search for existing literature | Organisational and Ethical | | |

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| | | the communication about the technology? | (dependent, passive user), and possibilities (empowered, active user).. | | | | review, or collect primary studies and if possible conduct a litterateur review,or, if relevant data is not available, conduct a primary study; if there's no time for primary study, the opinion of health care professionals, patients, citizens, or important others can be consulted. | Domains | | |

## 9 Legal aspects

| ID | Topic | Issue | Clarification | Import. | Transf. | Is core | Methodology | Content relations | Sequential relations | References |
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| I0002 | Autonomy of the patient | What kind of legal requirements are there for providing appropriate information to the user or patient and how should this be addressed when implementing the technology? | Describe the rules and recommendations about what patients should know of the implications of using or not using the technology. The right of the patient to not-to-know may also be important, as well as patient's right to complain. These rules are likely to be helpful for the persons involved in implementing the technology to prepare proper information and counselling. This information may be particularly important with technologies carrying high risks of harm, technologies with potential to provide information that is not directly relevant to the condition being tested, and in emergency situations in which the patients does not usually have sufficiently time to consider the treatment decision. | Critical | Partial | Yes | Convention on Human Rights and Biomedicine CETS No: 164 (including the Explanatory report to Biomedicine convention).<br><br>Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare, National laws specially on patients' rights.<br><br>Additional Protocol to the Convention on Human Rights and Biomedicine | B0014, B0015, C0002, C0005, C0007, C0008, F0004, F0006, F0010, F0016, G0004 | B0014, B0015, C0002, C0005, C0007, C0008, F0004, F0010, G0004 | EU Charter of fundamental rights (2000/C 364/01) Art 3;<br><br>Biomedicine Convention Art 5 |

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| | | | | | | | concerning Genetic Testing for Health Purposes, CETS No. 203. | | | |
| I0034 | Autonomy of the patient | Who is allowed to give consent for minors and incompeten t persons? | In law, a minor is a person under a certain age—usually the age of majority—which legally demarcates childhood from adulthood. The age of majority depends upon jurisdiction and application, but is generally 18. An incompetent person may be defined as one whose mind is unsound, deranged, or impaired in function, such as a slow I.Q., deterioration, illness or psychosis. What do laws/binding rules require when considering informed consent in these groups. See also I0002. | Important | None | No | Convention on Human Rights and Biomedicine CETS No.: 164 (including the Explanatory report to Biomedicine convention).<br><br>National laws on patients' rights.<br><br>Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes, CETS No.: 203.<br><br>Directive | F0005, I0002 | F0005, I0002 | Convention on Human Rights and Biomedicine, Art 6 and 7 |

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| | | | | | | | 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data, OJ 1995 L 281/31. | | | |
| I0007 | Privacy of the patient | Is there a possibility that the use of the technology produces such additional information that is not directly related to the current care of the patient and may violate her right to respect for private life? | The protection of sensitive personal data is secured at the EU level. Privacy protection is a modern expression of the ancient ethical principle of confidentiality in doctor-patient relationship. The use of computerised patient record databases and modern genetic diagnostics mean challenges to this principle. As an example Z vs. Finland (ECHR February 25, 1997): This is about a case of an HIV infected person, where the HIV positive test was an incidental finding, not-related to her healthcare | Important | Partial | Yes | Case laws, medical case reports. Z vs. Finland (ECHR February 25, 1997); M.S. vs. Sweden (ECHR August 28, 1997); national legislation; legal literature. | B0012, C0006, D0022, F0101 | C0006, D0022, F0101 | Directive 95/46/EC, EU FR Charter Art 8, Biomedicine Convention Art 10, CM Recommendation R (97) 5. European Convention on Human Rights CETS No.: 005 art. 8 |

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| | | | intervention. | | | | | | | |
| I0009 | Privacy of the patient | What do laws/ binding rules require from appropriate measures for securing patient data and how should this be addressed when implementing the technology? | Provide an overview of the legal requirements, regarding policies and procedures, and examples of practical local solutions, of securing the kind of patient data that will be generated when using of the technology. Who is allowed to save and store the patient-data, where is it saved, for how long, and who can have access to it? Does the use of the technology produce some additional (i.e. diagnostically or therapeutically irrelevant) information on the patient that could be relevant for e.g. health insurance, marketing studies, or safety authorities and how should data protection be handled in these cases? Is it possible that legal data protection requirements have adverse consequences to the quality of care, e.g. by complicating the transfer of patient data in a screening process, and how should this be addressed? | Important | Partial | Yes | Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.<br><br>Convention on Human Rights and Biomedicine CETS No.: 164 (including the Explanatory report to Biomedicine convention).<br><br>Recommendation R (97) 5 of the Committee of Ministers to Member States on the protection of | B0010, F0101, F0016 | B0010, F0101, F0016, | Directive 95/46/EC; Convention on Human Rights and Biomedicine Art 10, |

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| | | | | | | | medical data.<br><br>National laws specially on patients' rights and data protection.<br><br>Z vs. Finland (ECHR February 25, 1997); M.S. vs. Sweden (ECHR August 28, 1997). | | | |
| I0011 | Equality in health care | What do laws/ binding rules require from appropriate processes or resources regarding guaranteein g equal access to the technology? | In general, equality in health care is spoken out in the EU Charter of Fundamental Rights and it is also one of the central principles of the Biomedicine Convention. Moreover, in many Constitutions equality of citizens covers also access to health care. However, there may be experiences nationally of some specific difficulties in equal access to the technology, and probably also proposed solutions, which could be helpful for decision makers in other countries too. | Critical | Partial | Yes | Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare.<br><br>Recommendati on R (2006) 18 of the Committee of Ministers to Member States on health services in a multicultural | F0012, F0014, F0016, G0009, G0101, H0012 | F0012, F0014, F0016, G0009, G0101, H0012 | EU FR Charter Art 35, Biomedicine Convention Article 3, CM RecommendationR (2006) 18 |

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| | | | | | | | society.<br><br>National laws.<br><br>Additional Protocol to the Convention on Human Rights and Biomedicine concerning Genetic Testing for Health Purposes, CETS No.: 203.<br><br>Case law: S.H. and others vs. Austria (ECtHR April 1, 2010).<br><br>Gillberg vs. Sweden (ECtHR November 2, 2010).<br><br>Commission vs. France (ECJ C-512/08) of October 5, 2010.<br><br>R.R. vs. Poland (ECtHR | | | |

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| | | | | | | | May 26, 2011)<br><br>Panaitescu vs. Romania (ECtHR Apri 10, 2012).<br><br>Costa and Pavan vs. Italy (ECtHR August 28, 2012) | | | |
| I0012 | Equality in health care | What are the consequences of various EU level and national regulations to the equal access to the technology? | The possible consequences of the EU Directive of cross border health care could be considered here. There may be legally defined processes nationally, including reimbursement and pricing, determining the implementation and level of access of a technology. This information may give useful insight also beyond one's own country. | Important | Partial | Yes | Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 on the application of patients' rights in cross-border healthcare.<br><br>National laws. | A0021, B0004, F0012, F0013, G0009, G0101, H0012, H0015 | A0021, B0004, F0012, F0013, G0009, H0012, H0015 | Charter of Fundamental Rights of the European Union (2000/C 364/01). Art 35 |
| F0014 | Ethical aspects | Does the implementation or use of the technology affect the realisation of basic human rights? | The basic human rights are most notably declared in the United Nations Declaration of Human Rights (Ref: http://www.un.org/en/documents/udhr/). They are universal and consider the most important goods, protections and freedoms for mankind. For HTA, perhaps the most | Critical | Complete | Yes | Literature search. Law, rules and regulations. Expert opinion. Stakeholder hearing | SHARED between ethical and legal domains | H0012 | 49, 57 |

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| | | | relevant are the rights to equality, non-discrimination, safety, adequate standard of living and health care. | | | | | | | |
| F0016 | Ethical aspects | Can the use of the technology pose ethical challenges that have not been considered in the existing legislations and regulations ? | Is legislation and regulation to use the technology fair and adequate? Use of the technology may lead to ethical issues that make current regulations inadequate. Screening and diagnostic technologies are commonly differently regulated than treatments, especially medications. Ethical reflection is essential in order to assess what kind of legislation, regulation or amendments is needed (see also legal domain). | Important | None | No | Law, rules and regulations. Stakeholder hearing. Expert opinion | SHARED between ethical and legal domains | B0010, I0011, I0009, I0002, I0026 I0037 | 49, 58 |
| I0015 | Authorisation and safety | What authorisations and register listings does the technology have? | Describe here the register listings, both at EU level and national level, which might be relevant when implementing the technology and planning e.g. local authorisation, monitoring or evaluation functions, as well as qualification and quality control. Examples include technology registers, registers for marketing authorisation, certification of safety and reimbursement. | Important | Complete | Yes | Directive 2004/23/EC of the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, | A0020, B0010, C0002, C0007, C0060 | A0020, B0010, C0002, C0007, C0060 | In vitro diagnostic directive (98/79/EC); EUDAMED; FDA, EMA |

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| | | | However, some of the registers, e.g. the one for medical devices (EUDAMED), are not open for HTA doers. Information of register listings may be particularly relevant for the technologies which can be used off-label or as investigational intervention outside clinical trials (so-called expanded access or compassionate use). | | | | preservation, storage and distribution of human tissues and cells.<br><br>Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.<br><br>National laws.<br><br>Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use | | | |
| I0017 | Authorisation and safety | What do laws/ binding rules require from the safety | What are the legal requirements for safety of the technology and quality of care; does the technology fulfil these requirements; and | Critical | Complete | Yes | Results from Safety domain.<br><br>Directive 2004/23/EC of | B0002, B0003, B0008, C0002, C0020, | B0002, B0003, B0008, C0002, C0020, | Directive 93/42/EEC, Directive 2001/95/EC |

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| | | of the technology and how should this be addressed when implementing it? | what should be done to ensure that the legal requirements maintain fulfilled when implementing the technology? The findings of the safety and organisational domain should be considered here in the light of relevant European or national safety regulations. See also I0015. | | | | the European Parliament and of the Council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells.<br><br>Directive 2001/95/EC of the European Parliament and of the Council of 3 December 2001 on general product safety.<br><br>Council Directive 93/42/EEC of 14 June 1993 concerning medical devices.<br><br>National laws. | C0040, C0062, C0063, C0064, G0012, I0015 | C0040, C0062, C0063, C0064 | |

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| | | | | | | | Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products | | | |
| I0019 | Ownership and liability | What should be known about the intellectual property rights and potential licensing fees? | This information is important because infringement of intellectual property rights can reduce the use of the technology and have implications in the wording of the acquisition contract of a new technology, and possibly also licencing fees. | Important | Complete | Yes | Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions.<br><br>Directive 2004/18/EC of the European Parliament and of the Council of 31 March 2004 on the coordination of procedures for the award of public works contracts, public supply | | | 2004/18/EC on public contracts.<br><br>European patent convention (EPC), Directive 98/44/EC, national legislation |

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| | | | | | | | contracts and public service contracts.<br><br>National laws.<br><br>Patent data bases.<br><br>Manufacturer's information.<br><br>C-317/05 (ECJ) | | | |
| I0021 | Ownership and liability | What should be known of the legal or binding rules about the width, depth and length of the manufacturers guarantee | This issue may help the decision maker to be aware of their legal rights when considering the manufacturers guarantee. User guide plays part in determining the manufacturer's liability. | Optional | Complete | No | Manufacturer's information<br><br>Sales/purchase contract | | | National laws about manufacturer guarantee |
| I0023 | Regulation of the market | What kind of legal price control mechanisms are there relevant to the technology? | Describe the adopted economic measures to control public health expenditures when adopting technologies. This information, although not transferable, gives insight to decision maker in other | Critical | Partial | Yes | Directive 2004/18/EC of the European Parliament and of the Council of 31 March 2004 on the coordination of procedures for | G0007 | G0007 | Directive 1989/105/EEC |

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| | | | countries too. | | | | the award of public works contracts, public supply contracts and public service contracts.<br><br>Council Directive 89/105/EEC of 21 December 1988 relating to the transparency of measures regulating the prices of medicinal products for human use and their inclusion in the scope of national health insurance systems.<br><br>National laws.<br><br>C-317/05 (ECJ), T-179/00 (ECJ) | | | |
| I0024 | Regulation of the market | What kind of regulation exists for | Expensive technology and dangerous pharmaceuticals are typically subject to | Critical | Partial | Yes | Directive 2004/18/EC of the European | G0006, G0007 | G0006, G0007 | Directive 2004/18/EC |

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| | | acquisition and use of the technology? | acquisition regulation. | | | | Parliament and of the Council of 31 March 2004 on the coordination of procedures for the award of public works contracts, public supply contracts and public service contracts.<br><br>National law.<br><br>Case law: Commission vs. Poland (ECJ C-185/10) of March 29, 2012.<br><br>Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use | | | |

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| I0025 | Regulation of the market | What legal restrictions are there for marketing the technology to the patients? | Describe here the general legal principles of the restrictions of marketing health technologies to lay people. | Critical | Partial | Yes | Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices.<br><br>Directive 93/42/EEC of 14 June 1993 concerning medical devices.<br><br>Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices.<br><br>National laws<br><br>Directive 2001/83/EC of the European | | | Directive 1989/105/EEC, directive 2001/83/EC |

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| | | | | | | | Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use | | | |
| I0026 | Regulation of the market | What should be known about the legal issues in cases of new technologies where the current legislation is not directly applicable? | Novel technologies may not always be unambiguously covered by existing legislation. Sometimes an otherwise restricted technology can be used in clinical trials or as "compassionate use", i.e. in extended use outside clinical trials. Important questions, such as 'how are the liability issues solved according to existing legislation?', or, 'is the voluntary participation of patients guaranteed properly?' may be important to consider. If the current law does not provide a straightforward answer to the liability issues it may be advisable to consult a legal expert on the interpretation of the existing provisions with regard to the technology in question. Sometimes even new legislative measures are | Critical | Partial | Yes | Consulting legal expert, possibility to analogical interpretation of law, Court decisions, literature | B0002, B0003, F0003, F0016 | B0002, B0003, F0003, F0016 | |

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| | | | needed. | | | | | | | |
| I0037 | Regulation of the market | Are there relevant concerns of conflicts of interest concerning the preparation of binding rules and their implementation? | Relevant concerns of partiality or conflicts of interest regarding binding guidance may give useful insight to decision makers about the importance of implementing a technology. | Critical | Partial | Yes | Literature | | | Decision No 1926/2006/EC of the European Parliament and of the Council of 18 December 2006 establishing a programme of Community action in the field of consumer policy (2007-2013)<br><br>http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32006D1926&from=DE (2.4.2014)<br><br>Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (especially (4), (6), Art 13 (1., 3a, 3b).<br><br>http://eur- |

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