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PhD Thesis

Developing and Evaluating Strategies to Support Informed Decisions and Practice Based on Evidence

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The right of science means
the right to access the benefits of science,
the right to contribute to science,
and the right to take part in decision-making about science in general.

Richard Horton
(The Lancet, October 2013)

to Alessandro Liberati,
a mentor and a friend

Acknowledgements

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Table of Contents

List of abbreviations

HTA: Health Tecnhology Assessment

WP: work-package

EtD: Evidence to Decision framework

PICO: Population, Intervention, Comparison, Outcomes

SR: Systematic Review

CG: Clinical Guideline

RCT: Randomised Control Trial

AB: Advisory Board

SoF: Summary of Findings table

iEtD: interactive Evidence to Decision table

Abstract

Background: Today health systems are offered with a wide range of interventions and technologies with the uncertainty about their relevance for people's health, so making decisions timely, informed by the best evidence and taking into account all the dimensions needed for their formulation it's quite difficult. Moreover the considerable amount of research literature and the fact that it is sometimes contradictory and presented in a way that is difficult for non-researchers to understand contribute to the complexity of the decision-making. Clinical practice guidelines and HTA reports represent a good source of support in this process. However decisions should be influenced not only by the best estimates of the benefits and harms but also by other factors such as confidence in these estimates (quality of the evidence), patient values, resource use, feasibility and equity. More effective communication strategies are needed to bridge the gap between clinical research and decision-making in healthcare.

Objectives: Main objective of this project was the development of an appropriate "conceptual framework" which include criteria identified as necessary to inform the process that goes from the assessment of evidence to decisions.

Methods: This project is part of a wider research program called DECIDE: Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence (www.decide-collaboration.eu). It is funded by the European Community and, starting from the GRADE methodology (www.gradeworkinggroup.org), aims to develop strategies for dissemination and communication of scientific evidence to support decisions of clinical practice and health policy. Communication strategies are developed specifically for different "target audiences" taking into account the variability of information needs that characterize them. In particular, this project focuses on the activity of one of the 8 work-packages of DECIDE (WP2) that is specifically targeted to policy makers and managers and their support staff with responsibility for making coverage decisions. These coverage decisions are defined as decisions by third party payers (public or private health insurers) about whether and how much to pay for drugs, tests, devices or services and under what conditions and can take place at national and/or regional level depending on the type of interventions. The initial development of an optimal presentation format was based on the work of the GRADE working group and includes: review of the existing literature,

brainstorming workshops to generate ideas and potential solutions, and collection of user' feedbacks and formal user-testing to inform revisions from a user perspective.

Results: An initial presentation of an Evidence to Decision (EtD) framework was developed.

The EtD includes a structured PICO question about the coverage decision to be taken, a concise summary with all the background information needed and a *table* with the following columns: *Domains (*factors that should be considered for coverage decisions); *Criteria* (specific aspects of each domain); *Judgements (*considerations that must be made in relation to each criterion taking into account the evidence available); *Research Evidence (*information about the research evidence available relevant for the decision); *Additional information (*any additional information, not "research evidence"). The final section of the EtD is designed to help summarise the information reported above and take the decision.

Practical examples of application of the EtD to real-life decisions were presented during interactive workshop to collect feedbacks about the usefulness of the tool.

Conclusions: Positive feedbacks were collected about the usefulness of the EtD. Further developments are needed to better refine some parts. Piloting in real life setting are needed to foster the dissemination of the EtD in the decision-making process.

Chapter 1: Overview of the Thesis

This Thesis describe the composite research work done within a European Project called DECIDE (www.decide-collaboration.eu).

Aim of the DECIDE Project is to optimize the spread of knowledge and use of evidence-based interventions in a sustainable way, move shared decision-making forward and reduce the use of interventions where benefits are uncertain, particularly in relation to harms through improving the dissemination of evidence-based recommendations by building on the

work of the GRADE Working Group (www.gradeworkinggroup.org).

Main product of the DECIDE Project is a conceptual framework that should help different stakeholders to go from evidence to decision (EtD).

In Chapter 2 background information about the aim of the project are reported. There's also a description of the general structure of the DECIDE Project, specific information about the work described in this thesis and an introduction to the activity of the GRADE Working Group.

Chapter 3 describes the methods used for the development of the EtD framework.

Chapter 4 describes the main features of the EtD framework analyzing each component and potential future developments.

An overview of the evolution of the EtD framework over time is available in the Appendices.

Chapter 2: Background

What matters in the real world is not the theoretical ethics of hard situations,
but the practical realities of real decisions.

Stephen Black
(The British Medical Journal, April 2011)

Healthcare decisions should be based on the best available research evidence, however, experience and literature describe a different situation. There are several reasons for this deficiency, above all the overwhelming amount of research literature sometimes contradictory and presented in ways difficult to understand especially for non-researchers [1, 2].

Systematic reviews (SR) are valuable sources of research evidence for informing healthcare decisions. They should be based on a comprehensive search for relevant studies and should include an appraisal of the methodological quality and reliability of these studies [3, 4]. Also Clinical Guidelines (CG) and Health Technology Assessment reports (HTA), that should be based on rigorous SR, represents good ways of summarizing and presenting evidence and/or recommendations to healthcare decision makers. However these products are usually developed as a one-size-fits all package with no attempt at tailoring the information for particular audiences or at exploring what different stakeholders need and want to support their decisions [5] leading often to difficulties for user's in understanding and using the evidence.

Moreover decisions are influenced not only by the best estimates of the expected advantages and disadvantages of an intervention but also by contextual factors, time constrains, values and local circumstances like availability of resources [6]. Evidence is essential, but not sufficient for effective and shared decision-making. In strengthening the local use of global evidence, all healthcare participants will need better access to evidence. In particular, they need evidence that has been synthesised and presented in ways that accommodate their needs and addresses barriers to their accessing the information they need when they need it.

The development and evaluation of dissemination strategies targeted to the different stakeholders involved in the healthcare decision-making process would help the transfer of evidence-based research findings into practice.

2.1 The DECIDE Project

The DECIDE project (http://www.decide-collaboration.eu) is a 5-year project funded within the 7° Framework Program of the European Commission. It started on the 1st of January 2011 and aims to build on the work of the GRADE working group (www.gradeworkinggroup.org) by developing and evaluating ways of effectively communicating and supporting the uptake of evidence-based recommendations in order to:

- optimize the spread of knowledge and use of evidence-based interventions in a sustainable way
- move shared decision-making forward
- reduce the use of interventions where benefits are uncertain, particularly in relation to harms.

The project is structured in five investigational work-packages (WP) each targeted to a different stakeholders' group of healthcare decision makers [7]:

- healthcare professionals (WP1)
- policymakers and managers (WP2)
- public, patients and carers (WP3)
- users of evidence on diagnostic tests (WP4)
- users of evidence on health system policies (WP5)

There are three other work packages in DECIDE: WP6 responsible for the development of a toolkit for preparing and disseminating evidence-based recommendations, WP7 dedicated to support communication and dissemination of DECIDE findings and WP8 in charge of the project management.

All WPs involve partners coming from European Countries and the World Health Organisation (WHO), moreover there's a strong collaboration with the GRADE Working Group, and the Guidelines International Network (GIN).

A list of the DECIDE partners is provided in Table 2.1.1.

The activity of the five investigational WPs concentrate on the development of different communication strategies, each focused on the needs of particular stakeholders' groups, to do that they work in synergy similar approaches. A graphical presentation of the collaboration among WPs is shown in Figure 2.1.1.

Table 2.1.1: DECIDE partners

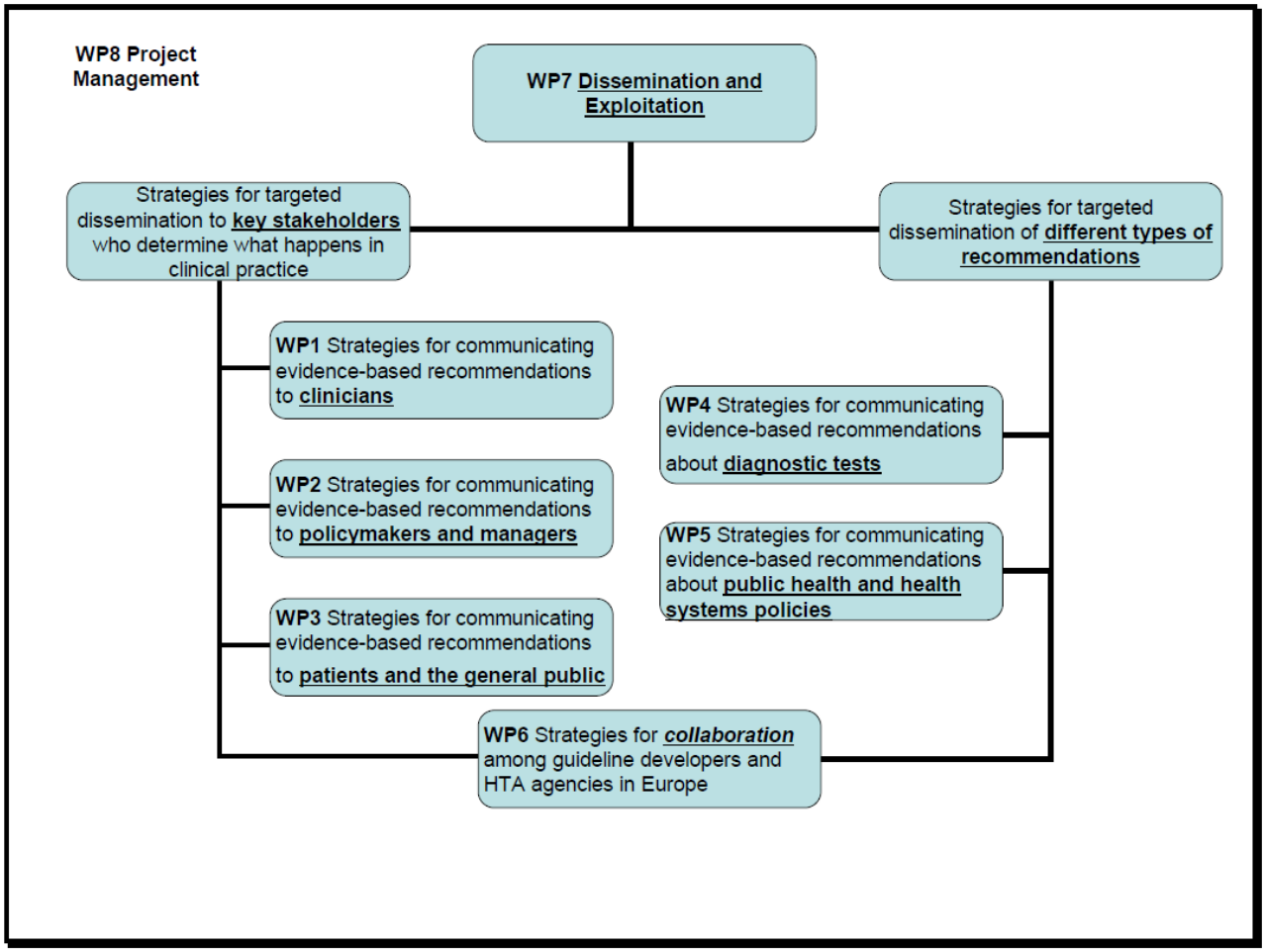
Partner N°	Organisation name	WP	Country
1	University of Dundee	WP8	United Kingdom
2	Norwegian Knowledge Centre for the Health Services	WP5	Norway
3	Biomedical Research Institute (IIB-Sant Pau)	WP1	Spain
4	Lazio Regional Health Service, Department of Epidemiology	WP2	Italy
5	University of Amsterdam	WP4	Netherlands
6	World Health Organisation	WP7	International
7	University Hospital, Freiburg	WP6	Germany
8	National Institute for Health and Clinical Excellence	Multiple collaborations	United Kingdom
9	Scottish Intercollegiate Guidelines Network	WP3	United Kingdom
10	Finnish Medical Society Duodecim	WP3	Finland
11	University of Aberdeen	WP7	United Kingdom
12	Italian Cochrane Centre	WP2	Italy

The organization of the work in DECIDE is structured in three phases:

- Phase 1- Strategy development: during this phase different methods (brainstorming, survey, stakeholder's feedbacks, user testing) are used to generate ideas and collect feedbacks from stakeholders in order to develop dissemination strategies targeted to specific audiences.
- Phase 2 - Evaluation of the strategies: during this phase the strategies developed are tested through comparative studies, preferably randomized control trials (RCT).

- Phase 3 - Testing the strategies with real guidelines: during this last phase strategies are applied in real health decisions' settings. Their impact is evaluated on outcomes such as knowledge, attitudes and self-reported behaviour using surveys and interviews.

Figure 2.1.1: Collaboration among DECIDE WPs



Main product of the DECIDE Project is a conceptual framework that should help different stakeholders to go from evidence to decision (EtD).

The work described in this Thesis focus primarily on the Phase 1 of the project.

2.2 WP2: strategies for policy makers and managers involved in coverage decisions

This work is based on the activity of WP2 of the DECIDE Project.

WP2 is led by the Department of Epidemiology of the Lazio Regional Health Service in collaboration with the Italian Cochrane Centre. The activity of this WP focus on the development of strategies to help decision makers in going from evidence to coverage decisions.

Coverage decisions are defined as decisions by third party payers (public or private health insurers) about whether and how much to pay for drugs, technologies, tests, devices or services and under what conditions. They can take place at national, regional or local levels, depending on the type of interventions and the way health services are paid for in a country. Often, commissions or panels of people, that may include policymakers, managers and support staff, researchers and healthcare professionals, make these decisions.

Like other healthcare decisions, coverage decisions are complex and require consideration of multiple factors [8]. Concerns on costs, effectiveness and cost-effectiveness of health interventions have dominated the debate in a wide range of countries since long [9]. More recently, the use of equity-related criteria [10, 11] have been put forward, like severity of disease, socio-economic status, or gender, reflecting the increased attention for distribution of health in a population. Furthermore other criteria, like ease of implementation or political acceptability are presently considered in the prioritization of health interventions [12].

A recent systematic review of coverage decision-making on health technologies [13] provided a summary of the available empirical evidence on determinants of real-world decisions. Decision-making is addressed very heterogeneously, and varies across countries [14]; only a few variables were identified that were used in several studies: specifications of the decision outcome, indications considered for appraisal, identification of incremental cost-effectiveness ratios, appropriateness of evaluation methods, type of economic or clinical evidence used for assessment, and the decision date.

The complexity of coverage decision-making – reflected by the heterogeneity of identified components – shows how a standardised and transparent approach to inform coverage decisions with the best available evidence can help to structure a well-informed and consistent decision-making processes, and to make explicit, clarify and resolve disagreements about coverage decisions.

Processes for deciding which drugs to cover have become increasingly systematic and evidence-based in many countries and often include economic evaluations. Whereas, coverage decision-making processes for other technologies and services is much more varied. Often coverage decisions focus on new technologies and services (interventions). However, increasingly attention is being given also to decisions about whether to stop coverage for interventions that are not effective or cost-effective [9].

Conflicting interests, particularly financial interests, can affect coverage decisions in undesirable ways [15]. For example, manufacturers want to ensure coverage to make a profit on their investment and are likely to lobby for coverage of their products (sometimes using clinicians or patient groups). For-profit third-party payers making decisions want to contain costs to ensure their profit, but may also want to ensure coverage in order not to lose enrolees, and politicians may want to avoid antagonising voters or lobbyists.

How coverage decisions are similar to and different from clinical recommendations

Coverage decisions and clinical recommendations share some common features. Both require formulation of a question, an assessment and conclusions. The question details require similar considerations. However, whereas guideline panels can make clinical recommendations from the perspective of an individual patient, coverage decisions are always made from a population perspective. The factors that affect a decision (criteria) are similar, but there are some important differences in relation to panels' judgements about how much people value the main outcomes, equity, acceptability and feasibility. Clinical recommendations must be made accountable to professional peers and to the individual patients affected by the clinical decision, in these conditions only the professional standing of the clinician is at stake. On the contrary a coverage decision is subject to the judgment of a population of relatively well informed stakeholders, vested interests and social representatives, in this conditions it is the political standing of the decision maker which is at stake, depending on volatile criteria of opinion consensus. Accountability is a strength of the coverage decision-making process as it confers openness and a chance of motivated disagreement. It is also a liability as it can lessen possible consensus through technicalities and it is amenable to possible misunderstanding.

Coverage decisions, like other priority-setting decisions, should be fair. This requires that they are relevant, transparent, possible to revise, and documented [16]:

- Relevance – The rationale for decisions should be based on the reasons (criteria and information) that 'fair-minded' people agree are relevant in the context
- Transparency – Decisions and the rationale for them should be publicly accessible
- Revisions – Ideally, draft priorities should be open to comment prior to finalising the decisions
- Documentation – The process used to set priorities should be documented. This ensures adherence to the agreed process and the fulfilment of the first three criteria

Main objective of the WP2 work is to develop instruments that may help to ensure that the coverage decision-making process adhere to these principles.

2.3 The GRADE System

The GRADE Working Group is an international group of guideline developers, health professionals, epidemiologists and statisticians that has developed an approach towards assessing and communicating the quality of evidence and the strength of recommendations (www.gradeworkinggroup.org). GRADE is now widely used. Some of the organisations that adopted this system are: the World Health Organisation, the Cochrane Collaboration, the UK National Institute of Health and Clinical Excellence (NICE), the Spanish Guideline National Programme of Guideline development, the Scottish Intercollegiate Guidelines Network (SIGN), The German Agency for Quality in Medicine, the Swedish Council on Technology Assessment in Health Care (SBU), the American College of Physicians (ACP), BMJ Publishing, Clinical Evidence and UpToDate (http://www.gradeworkinggroup.org/society/index.htm).

The novelty introduced by GRADE and its success relate to the systematic, explicit and transparent methodology adopted to rate the quality of evidence and the strength of the recommendation. Since the late 70s a growing number of organisations have employed various systems to rate the quality (level) of evidence and grade the strength of recommendations [17].This variability in systems and standards is confusing and slows down effective communication and transfer of research evidence into clinical practice. Main differences and strengths of GRADE compared to other existing systems are shown in Table 2.3.1.

Table 2.3.1: GRADE vs other systems of grading

Other systems	GRADE System
Implicit definitions of quality (level) of evidence and strength of recommendation	Explicit definitions - make clear what grades indicate and what should be considered in making these judgements
Implicit judgements regarding outcomes, the quality of evidence, balance between benefits and harms, and value of incremental benefits	Explicit judgements regarding which outcomes are important, the quality of evidence for each important outcome, the overall quality of evidence, the balance between benefits and harms, and the value of incremental benefits
The relative importance of outcomes considered implicitly	Explicit judgements about the relative importance of different outcomes
Balance between health benefits and harms not explicitly considered	Explicit consideration of trade-offs between important benefits and harms
Inconsistent summaries of the evidence	Consistent GRADE evidence profiles, including a quality assessment and a summary of findings
Seldom used by more than one organisation and little, if any empirical evaluation	International collaboration across a wide range of organisations in development and evaluation

GRADE is much more than a rating system. It offers a transparent and structured process for developing and presenting evidence summaries for systematic reviews and guidelines in health care and for carrying out the steps involved in developing recommendations. GRADE specifies an approach to framing questions, choosing outcomes of interest and rating their importance, evaluating the evidence, and incorporating evidence with considerations of values and preferences of patients and society to arrive at recommendations [18].

The GRADE's process for developing recommendations is summarized in Figure 2.3.1.

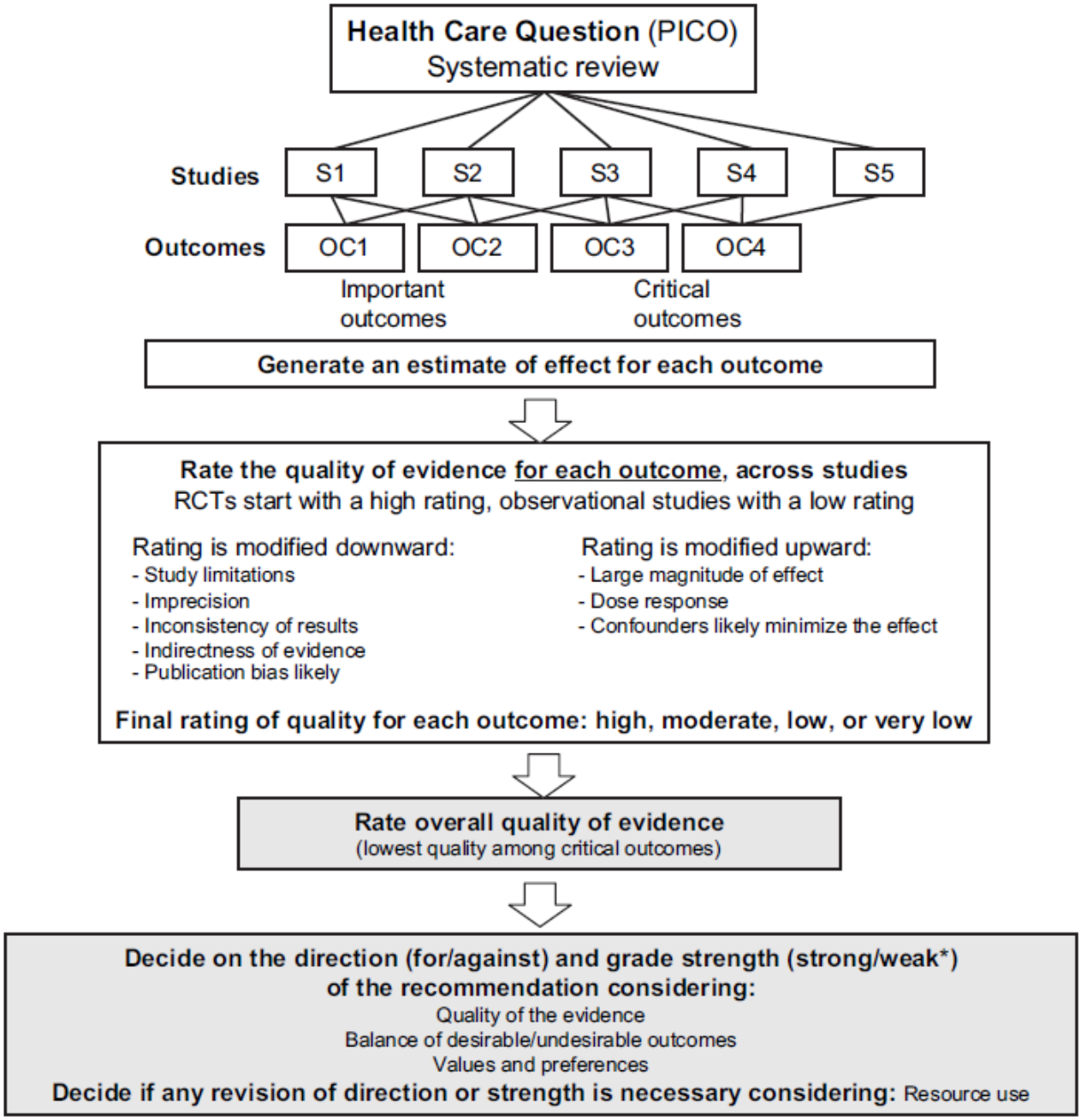
The process starts with the definition of the question according to PICO (population, intervention, comparison, outcome), then the outcome are classified as "critical" (for patient) or "important" but not critical. Through a systematic search of the literature relevant studies will be included to generate the best estimate of effect for each patient-important outcomes that will be then evaluated for their quality. In the GRADE approach, RCTs start as high-quality evidence and observational studies as low-quality evidence supporting estimates of intervention effects. Five factors may lead to rating down and three factors may lead to rating

up the quality. In the end, the quality of evidence for each outcome falls into one of four categories from high to very low [19]. The overall quality of evidence derived directly from the quality of each outcome (lowest quality among critical outcomes). The final step consist of deciding about the direction (determined by the balance between desirable and undesirable outcomes and patients' values and preferences) and the strength of the recommendation (determined considering, in addition to the other factors, the quality of evidence). Recommendations developed using the GRADE System may fall into four categories: strong positive, weak positive, strong negative and weak negative.

The GRADE system has been described for end users in a series of articles published in the Journal of Clinical Epidemiology between 2011 and 2013 [18].

The GRADE Working Group has also developed and evaluated ways of presenting concise summaries of the findings of systematic reviews (as the basis for recommendations or decisions) to health professionals, and has contributed to ways of presenting this information to policymakers and patients [20-22]. This work has been essential but does not address issues around how best to package and deliver GRADE recommendations to health professionals, policymakers, patients and others. DECIDE will therefore build on this work by developing and evaluating ways of effectively communicating and supporting the uptake of evidence-based recommendations (and the basis for such recommendations). This work will advance the state-of-the-art by taking the successful GRADE system and providing new research data on the most effective ways of using GRADE to develop and disseminate research evidence to healthcare decision makers.

Figure 2.3.1: GRADE' s process for developing recommendations [18]



Chapter 3: Strategies development

Data-driven decisions tend to be better decisions.

Andrew McAfee e Eric Brynjolfsson
(Harvard Business Review, September 2012)

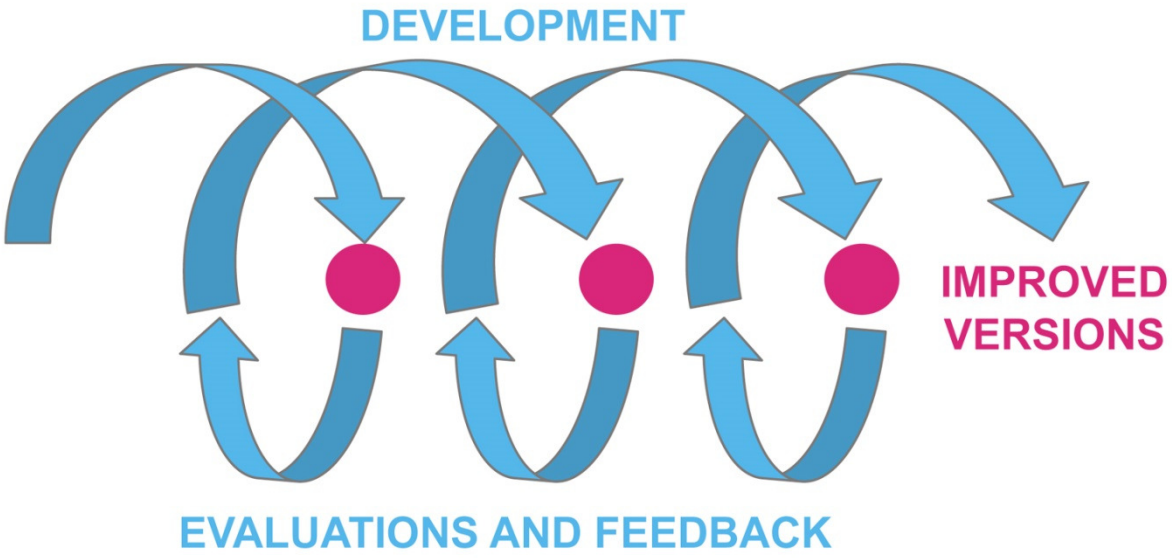
Our main objective is the development of a "*conceptual framework*" which include criteria identified as necessary to inform the process that goes from the assessment of evidence to coverage decisions (EtD).

The process of development of the EtD, based on the work of the GRADE working group, includes:

- Brainstorming workshops to generate ideas and potential solutions
- Survey to explore stakeholders' preferences and attitudes
- Stakeholders feedback about the strategies developed
- User testing of potential users
- Review of the literature

All these strategies are used in parallel and iteratively (Figure 3.1).

Figure 3.1: Iterative development process



3.1 Brainstorming workshops

Eight brainstorming sessions were held (face-to-face or by teleconference) to discuss the different stages of the project: definition of the target audience, identification of the main features of the conceptual framework, problems and ways of improving the format, suggestion of practical examples of coverage decisions. During the first session we started the discussion exploring the literature available on the topic and in particular using examples of SUPPORT Summaries for policy makers (http://www.support-collaboration.org) to identify critical elements and ways of improvements of the existing products. In the subsequent brainstorming sessions we started drafting the conceptual framework trying to identify the elements that should be included in it.

The participation to the brainstorming sessions involved WP2 members, other DECIDE partners, members of the GRADE Working Group and a selected group of Italian policymakers and managers which bring their own experience for the development of the conceptual framework.

3.2 Survey

Once we identified a first set of 9 criteria deemed to be crucial for going from evidence to coverage decisions, we conducted an international online survey of a diverse group of stakeholders involved in decision-making process and we asked about perceptions of criteria relevant to making coverage decisions, use of evidence and grading systems.

The survey aimed to collect information regarding the experience and perceptions of participants with respect to the proposed criteria within the EtD framework.

3.2.1 Methods

We asked DECIDE partners to help us in identifying approximately 10 people each in order to involve representatives from different EU countries.

Inclusion criteria for survey participants included people responsible for coverage decisions and stakeholders with an interest in and experience with coverage decisions, defined as decisions by third party payers (public or private health insurers) about whether and how much to pay for drugs, tests, devices or services and under what conditions. These type of

decision can take place at national, regional or local levels, depending on the type of interventions and the way health services are paid for in a country. Often, committees or panels of people, that may include policymakers, managers, clinicians and researchers, make these decisions.

We prepared an online survey in English and in Italian. A brief introduction with information about the DECIDE Project and the scope of the survey and a preliminary draft of the EtD framework were provided. At the beginning participants gave information on their role and type of training and were asked to list the last (maximum three) coverage decisions they were involved in. Then they had to rate whether each of the nine criteria in the EtD (severity of the problem, benefits, harms, quality of the evidence available, value, feasibility, impact on equity, cost-effectiveness and budget required) had been considered as part of the coverage decisions they were involved on a 3-point scale (yes, no, unsure). Participants were also asked to rate the importance (important, probably important, not sure, probably not important, not important) of each of the 9 criteria and their potential impact on the decision, and whether there were other important factors (not listed in the EtD) to be considered.

We asked participants also about the importance of including certain types of information in the EtD, like: effect sizes both quantitative and qualitative, confidence intervals, numbers of studies, and the quality of the evidence, their importance should be rated on a 5-point scale (1=not important; 5=extremely important).

The survey included also questions about the content and usefulness of the EtD framework.

Participants were contacted by email and asked to complete the online survey. They were provided with a personal code, answers were then de-identified for the analysis. Non-responders received a first reminder via email two months after the first contact and a second one 6 months later.

The survey questionnaire is available in Appendix 1.

3.2.2 Results

We contacted a total of 120 people (18 from UK, 8 from Spain, 11 from Netherlands, 27 from Norway and 56 from Italy). The response rate was just 22 % (26) and only 42% of the responses were complete.

Table 3.2.1 describes the characteristics of survey participants who provided background information (n = 21). Most of the respondents had medical training (62%), worked at national agencies (52%) and had managerial roles (76%).

The most common type of coverage decisions they were involved in was about drugs (69%).

Table 3.2.1: Characteristics of survey participants

	Participants n (%)
Total respondents	26
Providing characteristics information	21 (80,76)
Training	
Physicians	13 (61,90)
Pharmacists	3 (14,28)
Health economists	4 (19,04)
Administratives	1 (4,76)
Institution membership	
Institute/National agency	11 (52,38)
University hospital	2 (9,52)
Public hospital/clinic	4 (19,04)
Private hospital/clinic	1 (4,76)
NGOs	1 (4,76)
Pharmaceutical association	1 (4,76)
National commissioning group	1 (4,76)
Role/position held	
Managerial	16 (76,19)
Researcher	2 (9,52)
Clinician	1 (4,76)
Member of commissions	1 (4,76)
Type of coverage decision supported (N=13)	
Drugs	9 (69,23)
Organisational	2 (15,38)
Device/new technology	1 (7,69)
Surgery	1 (7,69)

Table 3.2.2 shows their responses regarding whether the 9 criteria proposed in the EtD were considered for their coverage decisions. Seven of our criteria (severity, benefit, quality of the evidence, value, feasibility, cost-effectiveness and budget) were taken into account by over the 75% of respondents (12), except for harms (58%) and impacts on equity (42%). Comments were infrequent.

Table 3.2.2: Criteria taken into account for the listed coverage decisions (N=12)*

Criteria	Yes (%)	No (%)	Unclear (%)
Severity	10 (83,33)	0	2 (16,66)
Benefits	10 (83,33)	0	2 (16,66)
Harms	7 (58,33)	3 (25)	2 (16,66)
Quality of evidence	9 (75)	1 (8,33)	2 (16,66)
Values	10 (83,33)	1 (8,33)	1 (8,33)
Feasibility	9 (75)	2 (16,66)	1 (8,33)
Equity	5 (41,66)	4 (33,33)	3 (25)
Cost-effectiveness	9 (75)	1 (8,33)	2 (16,66)
Budget	10 (83,33)	1 (8,33)	1 (8,33)

* Since each respondents had 3 answers for each criteria (see the survey questionnaire in Appendix 1), percentages were calculated considering the answer given at least two out of three times. When no answer was given more than once then we considered it as "uncertain".

Respondent ratings on the importance of the ten criteria are summarised in Table 3.2.3. All the criteria were judge as important for making a coverage decision by at least 50% of respondents (14), except for value (28%) and all of them were considered as having a sure or possible impact on coverage decision (see Table 3.2.4).

Respondent ratings on the importance of information regarding the effect of an intervention are described in Table 3.2.5. There was no general agreement on the relevance of the type of information reported: answers were split between extremely important or not important for almost all the options (eg. quality of evidence: not important 42%, extremely important 42%).

Most respondents (82%) agreed that a system of grading evidence would be desirable to inform policy makers responsible for coverage decisions and found the EtD framework a potential useful tool for this process.

Table 3.2.3: Importance of the EtD criteria for coverage decisions (N=14)

Criteria	Important (%)	Probably important (%)	Not sure (%)	Probably not important (%)	Not important (%)
Severity	11 (78,57)	2 (14,29)	0	1 (7,14)	0
Benefits	10 (71,43)	4 (28,57)	0	0	0
Harms	7 (50)	5 (35,71)	1 (7,14)	1 (7,14)	0
Quality of evidence	11 (78,57)	3 (21,43)	0	0	0
Values	4 (28,57)	4 (28,57)	3 (21,43)	2 (14,29)	1 (7,14)
Feasibility	7 (50)	5 (35,71)	0	2 (14,29)	0
Equity	7 (50)	4 (28,57)	2 (14,29)	1 (7,14)	0
Cost-effectiveness	12 (85,71)	2 (14,29)	0	0	0
Budget	8 (57,14)	5 (35,71)	1 (7,14)	0	0

Table 3.2.4: Importance of the EtD criteria for coverage decisions (N=14)

Criteria	Cover (%)	More probably cover (%)	Not relevant (%)	Less probably cover (%)	Not cover (%)
If the problem is serious you would choose to…	3 (21,43)	7 (50)	4 (28,57)	0	0
If the benefits are large you would choose to…	1 (7,14)	12 (85,71)	1 (7,14)	0	0
If the risk of undesirable effects is small you would choose to…	1 (7,14)	10 (71,43)	3 (21,43)	0	0
If the overall certainty of the evidence is high or moderate you would choose to…	2 (14,29)	10 (71,43)	1 (7,14)	1 (7,14)	0
If desirable effects are large relative to undesirable (pts view) you would choose to…	3 (21,43)	7 (50)	3 (21,43)	0	1 (7,14)
If the option is feasible to implement you would choose to…	2 (14,29)	9 (64,29)	2 (14,29)	1 (7,14)	0
If inequities could be reduced you would choose to…	3 (21,43)	8 (57,14)	3 (21,43)	0	0
If cost per unit of benefit is low you would choose to…	10 (71,43)	4 (28,57)	0	0	0
If impact on budget is low you would choose to…	4 (28,57)	9 (64,29)	1 (7,14)	0	0

Table 3.2.5: Importance of different type of information (N=12)

Criteria	5* (%)	4 (%)	3 (%)	2 (%)	1 (%)
Quantitative results	4 (33,33)	2 (16,66)	0	1	5 (41,66)
Confidence intervals	4 (33,33)	2 (16,66)	0	3 (25)	3 (25)
Qualitative results	2 (16,66)	2 (16,66)	5 (41,66)	0	3 (25)
Number of studies and/or participants	4 (33,33)	2 (16,66)	1 (8,33)	1 (8,33)	4 (33,33)
Quality of the evidence	5 (41,66)	1 (8,33)	1 (8,33)	0	5 (41,66)

* (5=extremely important; 1=not important)

3.2.3 Conclusions

Due to the poor response rate, the results of the survey couldn't be analysed extensively. The responses received were quite positive about the content and the possible usefulness of the EtD, but further investigations are needed to better understand the perceptions of stakeholders about it.

We've tried to envisage reasons for the low response rate and we identified some limitation in the way the survey was conduct: first of all it is possible that some of the questions seemed more complicated than necessary (eg. How important would you say it is to consider each of the following criteria when making a coverage decision? And how would they impact on them?); secondly the time between the first contact by email and the subsequent reminders were too long; and then we had some problem with the platform used for the online survey and, even if they were fixed quite rapidly, it is possible that they discouraged people to log in again.

3.3 Stakeholders feedbacks

Priorities and presentation formats were informed by means of consultation with key stakeholders. To do that we ask DECIDE Project' partners to suggest possible stakeholders for WP2 to constitute an international Advisory Board (AB). Our AB consists of 45 people with different backgrounds (policy makers, managers, health services researchers, methodologists, communication experts) and were purposely selected to ensure a breadth of perspectives.

We contacted the AB members approximately once a year by email, encouraging them to provide their feedbacks on the conceptual framework.

Moreover we contacted potential stakeholders during national and international meetings where the EtD was presented.

3.3.1 Methods

In order to collect stakeholders' feedback in a structured way, we prepared an online questionnaire on the main features of the EtD exploring dimensions such as comprehensiveness, relevance, applicability, simplicity, logic, clarity, usability, suitability, usefulness and specific strengths and weaknesses (See Appendix 2).

We aimed at collecting suggestions and comments about the EtD that could be useful to ameliorate the product highlighting things that should be changed or revised, but also characteristics considered positive and innovative.

Accessing to the online questionnaire stakeholders had the possibility to have a look at some examples of practical application of the EtD to specific topics and they were also provided with a brief list of terms that could be useful for a better understanding of EtD's features.

3.3.2 Results

We had a total of 103 contacts accessing the questionnaire. The responses to the feedback questionnaire are shown in Table 3.3.1.

Table 3.3.1: Feedback questionnaire results

Dimension	Yes	Uncertain	No
Comprehensiveness (N=87) Are there important relevant factors that are missing from the framework? If YES list them in the comments section.	30 (34,48%)	16 (18,39%)	41 (47,13%)
Relevance (N=86) Are there criteria included in the framework that should not have been? If YES list them in the comments section.	9 (10,47%)	9 (10,47%)	68 (79,07%)
Applicability (N=87) Is the framework applicable to different types of coverage decisions?	54 (62,07%)	31 (35,63%)	2 (2,30%)
Applicability (N=85) Is the framework applicable to different types of decision-making processes?	54 (63,53%)	28 (32,94%)	3 (3,53%)
Simplicity (N=86) Is the framework more complicated than necessary?	6 (6,98%)	17 (19,77%)	63 (73,26%)
Logic (N=87) Is the framework organised in a logical way that is easy to understand?	75 (86,21%)	7 (8,05%)	5 (5,75%)
Clarity (N=87) Are the criteria labelled and explained in a way that is easy to understand?	58 (66,67%)	20 (22,99%)	9 (10,34%)
Usability (N=87) Would it be easy for people responsible for coverage decisions to use the framework?	44 (50,57%)	38 (43,68%)	5 (5,75%)
Suitability (N=84) Is the framework suitable for informing and helping people to make coverage decisions?	59 (70,24%)	24 (28,57%)	1 (1,19%)
Usefulness (N=87) Is the framework likely to be useful to people responsible for coverage decisions?	66 (75,86%)	20 (22,99%)	1 (1,15%)
Overall assessment (N=80) Overall, is the framework adequate for its intended purpose?	64 (80%)	14 (17,50%)	2 (2,50%)

Stakeholders generally liked the design and the structure of the EtD. The majority of them found the framework adequate for the intended purpose (80%) and gave positive judgments about its simplicity (73%) and usefulness (76%) .

According to the feedbacks collected all the factors included in the framework are relevant for taking coverage decision (79%) and are presented and organize in a clear (67%) and logic (86%) way that help the stakeholders through the process.

The structure of the EtD was also judged to be quite flexible and applicable to different types of coverage decisions (eg. different types of interventions, local vs regional, regional vs

national) paying attention to adapt the volume and type of information reported in the content to the differences in reimbursement scheme (62%).

The main criticisms relate to the comprehensiveness (47%) of the information reported: more detailed information are required for cost effectiveness, feasibility, production capacity, and contextual factors that impact on the decision-making process, such as ability to implement the procedure.

Also some concerns about the usability (51%) of the EtD by people responsible for taking coverage decisions emerged: methodological contents not always easy to understand, difficulties with conceptual understanding of the GRADE approach, the terminology used sometimes not well understood or liked.

The main strengths of the EtD according to our respondents seem to be the capacity of summarizing all the important information in a clear and logic way.

Weaknesses are envisaged regarding the complexity of some information reported and the need for more details for some criteria like cost-effectiveness, budget and feasibility.

3.3.3 Conclusions

The EtD generally received positive feedbacks in almost all the dimensions we wanted to explore (comprehensiveness, relevance, applicability, simplicity, logic, clarity, usability, suitability, usefulness and specific strengths and weaknesses). We collected also a good number of fruitful comments that were used to made some changes to the framework and refine the contents for some criteria.

3.4 User Testing

The process of development of the EtD also included a formal user testing of the strategies with representatives of our target audience. The user testing aimed at investigating more thoroughly first impressions, attitudes and thoughts of potential users

We followed a methodology used for similar work by one of the partner of the DECIDE Project (Norwegian Knowledge Centre for the Health Services) [23].

3.4.1 Methods

The user tests were performed individually and took approximately one hour. With the participant's permission, we audio-recorded each test, and an observer took notes. Using a semi-structured interview guide, we considered both immediate first impressions and detailed exploration. The interview guide was designed to explore six of the seven different facets of "user experience" as described in a model by Peter Morville (http://semanticstudios.com/user_experience_design):

Usability: relates to the correct understanding and ease of use;

Credibility: relates to how much user thinks EtD is trustable;

Usefulness: relates to how much it could help;

Desirability: relates to how much the users like it and desire to use it;

Findability: relates to how easy is to find the information of interest within the EtD;

Value: relates to the potential added value.

The seventh facet from this model – accessibility – was not addressed, as the EtD used during the interviews was in paper form so the online accessibility was not relevant.

The users' experience Honeycomb model by P. Morville is shown in Figure 3.4.1.

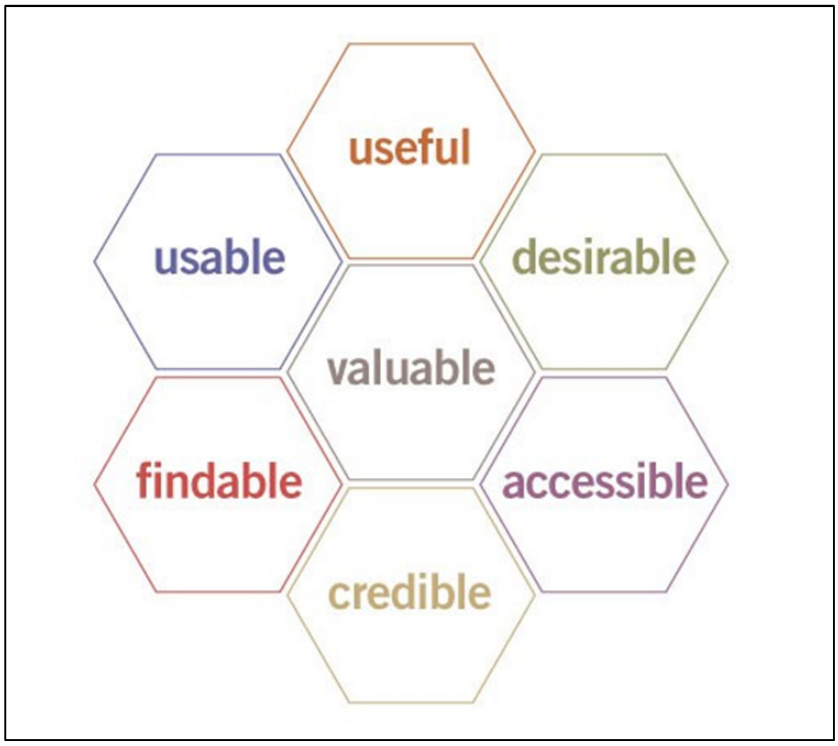
Follow-up questions covered overall impressions and suggestions for

improvement. The interview guide used for the user testing is shown in Appendix 3.

We reviewed all of the notes and recordings, looking primarily for barriers and facilitators related to correct interpretation, ease of use and favourable reception. We traced findings back to specific elements or characteristics of the EtD that appeared to facilitate or create problems. We rated findings in three categories according to the severity of the problem for

the user: major (causes incorrect interpretation, critical errors or high degree of uncertainty or dissatisfaction), medium (causes much frustration or unnecessarily slow use), minor (minor or cosmetic problems). We also registered nice-to-haves (things users explicitly liked) or suggestions for improvement.

Figure 3.4.1: Users 'experience Honeycomb model



3.4.2 Results

Eight people all coming from Italy took part in the user tests. Time for the interviews ranged from 1 hour to 1 hour and a half.

Characteristics of participants are presented in Table 3.4.1.

All participants but one had a medical background. Six of them had managerial roles in regional or local healthcare authorities and hospitals; two of them were members of commissions responsible for coverage decisions. Five out of eight had a formal training in research methodology (eg. master degree). All of them were at different levels involved in decision-making process about coverage.

Table 3.4.1: Characteristics of user testing participants

	Participants
Total	8
Background	
Medical	7
Economic	1
Trainig in research methodology	
Master degree	5
Role	
Manager in Regional Health Authorities	1
Manager in Local Health Authorities	4
Manager in a hospital	1
Member of national/regional commission	2

Overall the EtD received positive feedbacks. The first impression was always good and all the participants highlighted the logic structure and the systematic approach of the instrument.

The design of the EtD was generally appreciated. Minor problems related to the format of the examples provided (eg. printed on paper, several pages) and specific features (three participants suggested to move "judgments" in the last column) were pointed out.

Usability

"Usable" was the most used term to define the EtD at first sight, but going deeper in the analyses of single criterion some problems of usability emerged.

All participants but two (that were familiar with the GRADE System) had a first hesitation looking at the information reported for the Benefit and Harms criteria (SoF), but with a quick explanation of the main principles of GRADE they were all able to easily understand the SoF and the information reported.

Major to medium problems emerged for Values: three participants found the question "Is there important uncertainty about how much people value the main outcomes?" misleading, the others suggested to find a clearer way to detail that criterion.

Medium to minor problem of comprehension emerged also for Equity, Acceptability and Feasibility, mostly related to the lack of standardised methods to report information about them.

More details and information in the costs section, in particular for budget impact and local costs, were suggested by 5 participants.

Credibility

All participants found the EtD credible and appreciated the transparency of the process. One suggested to add information about the people who prepared it.

Usefulness and Desirability

The EtD was rated by all the participants from useful to very useful and all of them said they would be very keen if not enthusiastic to have the possibility to use it in their decision-making activity.

Findability

No problem related to findability emerged. All participants get confident with the instrument in a short time and it was quite easy for them to find information within the EtD.

Value

The added values of the EtD mentioned by all participants are the systematic approach applied to the decision-making process and the transparency and logic of the instrument.

One of the participants suggested also its potential educational role and the capacity of highlighting lack of evidence in specific areas.

3.4.3 Conclusions

In general the EtD framework received positive comments and was always seen as an interesting and innovative instruments. All the participants were potential users and they all stated that they would be keen to use it to take coverage decisions. This is promising for the further step of the project that include pilot testing in a real world setting.

Major to minor problems emerged for usability of the EtD related in particular to specific criteria, more than to general usability of the framework. The more problematic criteria are values and acceptability, but also for equity, feasibility and resource use some concerns

emerged. Next step of the project, evaluation of the EtD through comparative studies, should probably concentrate on these criteria trying to find the best way to present information about them considering comprehensiveness and ease of use.

The minor suggestions about cosmetic things and the structure will be probably solved by the development of an interactive format of the EtD framework (see "Future developments" section in Chapter 4).

Limitations

The main limitation of the user testing exercise is the small number of interviews performed. The reason for this is related to the development of the interactive format of the EtD (iEtD) by WP5 of the DECIDE Project that is almost completed. We decided to stop the user testing on paper format and to wait for the iEtD to go on for the interviews. Feedback received through the user testing on paper are used to inform the interactive version.

Another limitation of these results could be related to the characteristics of the participants: the majority of the them had a specific and advanced training in research methodology and two of the three persons that declared not to have had any specific training, had a long time work experience in research. For this reason they could be a selected population not representative of the majority of our potential users in the field of decision-making for coverage (in relation to their advanced research knowledge).

3.5 Review of the literature

During the development of the strategies we started collaborating with a group of researchers working on a project aimed at developing a conceptual framework for the adoption of new vaccines. The collaboration was really fruitful for both: for our group it represented the opportunity to try to apply the empirical work done within the DECIDE Project to a specific area, and for the vaccine group the chance to link their work to a wider international research program.

As first step of the collaboration we conducted a systematic review (SR) aimed at identifying and analyse existing frameworks and taxonomies on vaccines and vaccines adoption and connect these to the EtD framework.

Our group's role in the review process was mainly related to the analyses of the study retrieved and to the linkage between the SR findings and the EtD framework.

3.5.1 Methods

Inclusion criteria

SRs were included which summarized frameworks for vaccine adoption decision-making. A SR was defined as any review that mentioned the term ''systematic review'' in the title or abstract and/or reported the use of at least one bibliographic database (i.e., Medline) in the search process, having included both qualitative and quantitative studies [24]. To increase the comprehensiveness also primary studies (i.e., conceptual studies describing or proposing a set of decision criteria or a decision-making tool), which were not included in the selected SRs, were included.

Exclusion criteria: a) no frameworks for vaccine adoption decision-making or providing a narrow focus on a single criterion (e.g. cost-effectiveness studies); b) basic scientific research on vaccine development; and c) data pertaining to non-human vaccinations.

All relevant studies were included, regardless of their language or publication status.

Search methods

A systematic search between January 1990 and March 2013 was performed on the following bibliographic databases: MEDLINE, Embase, The Cochrane Library (i.e. Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Health Technology

Assessment Database, and NHS Economic Evaluation Database). The following keywords were used: *decision-making, vaccination, decision aid, model, framework, health policy, and immunization programs*. In order to consider primary studies that were not included in SRs a sensitive search strategy of MEDLINE, EMBASE and The Cochrane Central Register of Controlled Trials, between March 2010 and March 2013 (the final date of the searches reported in Burchett et al. [25], the most up-to-date SR on this topic) was performed.

In addition to bibliographic databases, also reference lists of all included studies and the following websites were searched: WHO, National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), European Centre for Disease Prevention and Control (ECDC) and Pan American Health Organization (PAHO).

Study selection

Two authors independently examined the titles and abstracts retrieved by the search strategy to remove obviously irrelevant or duplicate studies. The full-text articles of the potential relevant studies were independently assessed by the two reviewers to determine their eligibility in accordance to the inclusion criteria. Any disagreement among the reviewers was resolved by discussion. Reasons for exclusions were documented and a PRISMA flow diagram prepared [24].

Data extraction and management

The following information were extracted from each included study independently by two reviewers: purpose, publication date, origin and targeted country, primary results, decisional frameworks and taxonomy used. All doubtful information were presented to a third author and discussed before inclusion. Given the heterogeneity of study designs, their descriptive nature and lack of a standard methodology, their methodological quality was not assessed.

In a first step, we made an inventory and calculated the frequency of the proposed components about coverage recommendations found in the included studies.

In a second step we approached the proposed components adopting the EtD structure [7, 26] to align the terminology used in the vaccine frameworks to the ones of the EtD. In particular, we focused on trying to tabulate the resulting framework to present the information by dimensions and criteria as in the EtD.

3.5.2 Results

Search results

Search results are synthetized in Figure 3.5.1 We identified 2920 reference citations after excluding the duplicates. Among them, 98 potentially relevant publications were retrieved in full text. In the end we selected three SRs [25, 27, 28] and nine primary studies [29-37] not included in the SRs. In addition, we selected two SRs identified by hand searches [38, 39]. Thus, a total of 14 publications were included. For details about excluded studies see Appendix 4, Additional file 1.

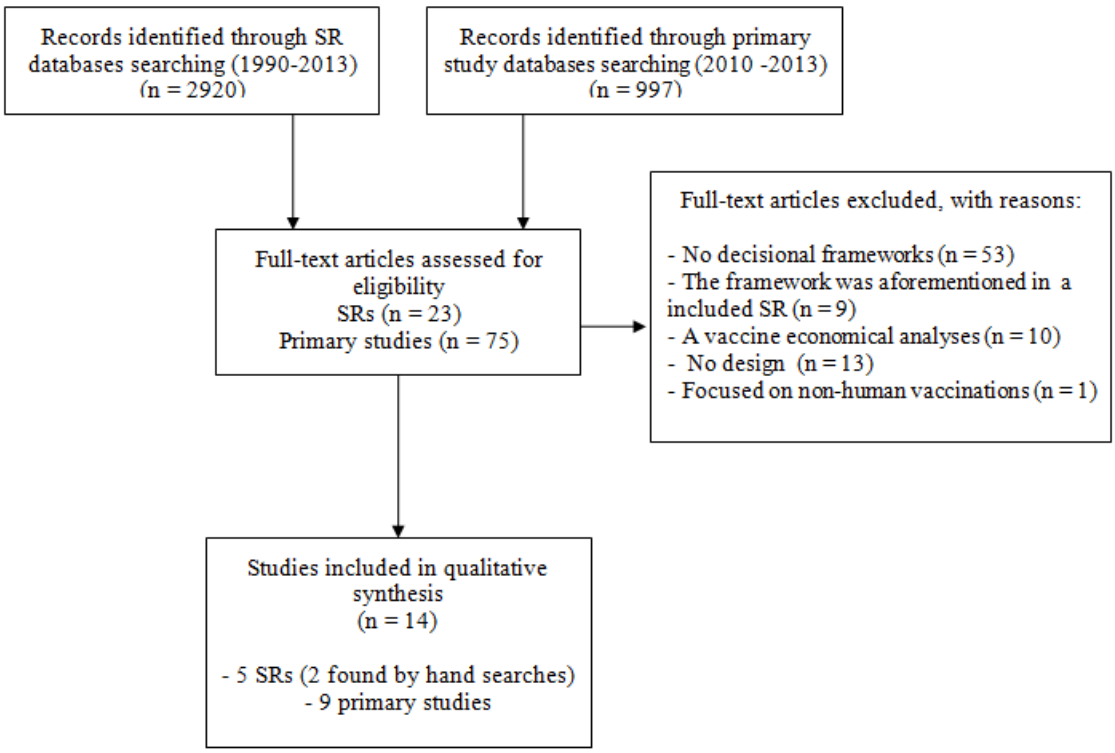
Description of SRs and primary studies included

All SRs included were published after the year 2000. All SRs were in English and originated from Canada, United Kingdom, Italy, Austria, and Mexico. The number of primary studies in each review ranged from five to eighty-five.

Two of the SRs were focused on developing a theoretical framework to support rational vaccination decision-making based on the available scientific literature, while the SRs of

Bryson et al. and Burchett et al. reviewed the literature on national decision-making regarding the adoption of new vaccines. The former included the presence and characteristics of National Immunization Technical Advisory Groups (NITAGs), which provide expert advice to government decision-makers. The latter analysed the frameworks included using a grounded theory approach to search for themes and categories that emerged from the criteria included. The review of Tapia-Conyer et al. assessed the evidence-basis of the Commission for the Future of Vaccines in Latin America (COFVAL) and feasibility in order to discuss each recommendation in the context of existing vaccine-preventable diseases control strategies.

Figure 3.5.1: PRISMA Flow diagram of search results



The 9 primary studies were in English language. Of these, 7 targeted different geographic and cultural context: 2 publications were focused on a middle-income country (South Africa), one on low-middle-income countries, 2 on the national immunization policy of developed and high-income countries (United States, South Korea), while 2 was applied to malaria-endemic countries. The other 2 studies were: one focused on accelerating the adoption of new vaccines in Global Alliance for Vaccines and Immunization (GAVI) eligible countries and one was based on the proposal of embracing the GRADE approach in the development of immunization related WHO recommendations.

The conceptual framework

First, for each publication, we extracted the dimensions and the criteria proposed or used (see Table 3.5.1). Additionally, it was reported the presence of a methodologically rigorous system. Then, after removing redundant terms of similar concepts (e.g., "economical and financial issues" or "economic data") within the studies, we identified ten dimensions repeated across the frameworks: *Importance of illness or problem, Vaccine characteristics (benefits and harms), Values and preferences, Resource use, Impact of vaccine, Acceptability, Feasibility, Equity and ethical considerations, Legal and political considerations, Decision-making.*

Table 3.5.1: Conceptual frameworks and empirical approaches analyzed

Studies	General description	Dimensions and criteria
Ahmed et al., 2011	The framework is based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.	- Balance of benefits and harms: review of the baseline risk for disease and the expected relative and absolute effects on vaccination on health outcomes. - Type of evidence: evidence is grouped into four categories, with the order reflecting the level of confidence in the estimated effect of vaccination on health outcomes. - Values and preferences: relative importance of outcomes related to benefits, harms and cost. - Health economic analyses: cost-benefit, cost-utility, cost-effectiveness.
Blecher et al., 2012 Ngcobo and Cameron 2012	The framework considers guidance and recommendations from WHO. The decision to introduce a new vaccine in South Africa is based on local data.	- Disease burden and public health priority: incidence, morbidity and mortality of the condition; the public health significance of the condition (Data reported by the National Department of health). - Efficacy and safety (Published studies in reputable international journal, if possible meta-analysis or Cochrane reviews). - Cost-effectiveness: local studies are usually required, given very different cost structures across countries. - Total cost and affordability: depends on fiscal space, prioritization, success in price negotiations and contracting. - Feasibility of implementation and availability of a credible implementation plan (If there are doubts about feasibility pilots studies may be useful). - International guidelines and advice of the South African National Advisory Group on Immunisation (NAGI) and other local and international experts. - Political process: besides the technical aspects, the budget process also involves communication between the Ministers of Health and Finance and approval by a wider committee of Ministers, the national Cabinet and Parliament.
Brooks and Ba Nguz2012 Milstien et al., 2010	The framework considers guidance and recommendations from WHO for introducing new vaccines for malaria.	- Malaria disease burden: reported and confirmed cases by age group; reported malaria-related deaths by age group; malaria epidemiology profile by district; malaria cases in pregnant women and HIV + population. - Other malaria interventions: impact of current malaria interventions; coverage of current malaria interventions; cost-effectiveness estimates of current malaria interventions. - Malaria vaccine impact: impact on mortality and morbidity by age group. - Economical and financial issues: cost-effectiveness estimates of malaria vaccine. - Malaria vaccine efficacy, quality and safety: adverse events; interaction with other vaccines; efficacy.
Bryson et al., 2010	Factors considered by countries when making recommendations by	- Burden of disease - Economic evaluation - Feasibility of local vaccine production

	presence of NITAGs.	- Feasibility of recommendation - Recommendations of other countries - Public perception - Vaccine safety and vaccine effectiveness
Burchett et al., 2012	Nine broad categories of criteria which may influence decisions on vaccine adoption.	- Importance of the health problem: burden of disease data, political priority, costs of disease, perceptions of importance. - Vaccine characteristics: efficacy, effectiveness, safety, deliver issues. - Immunisation programme considerations: feasibility, supply. - Acceptability - Accessibility, equity and ethics. - Financial/economic issues: economic evaluation, incremental costs, funding sources, vaccine price, financial sustainability, affordability. - Impact: impact on health outcomes and on non-health outcome, effect of co-administration, risks of serotype replacement. - Alternative interventions: cost –effectiveness of alternatives, effectiveness of alternatives. - Decision-making process: Evidence sources/quality of evidence, actors involved, procedures, cues to action.
Cho 2012	The framework considers guidance and recommendations from WHO for introducing new vaccines in Korea.	- Disease burden in Korea: clinical characteristics of the disease, incidence, mortality, and case fatality rates. - Analyzes data on the efficacy, effectiveness, and safety of the vaccine: Sources of information on the vaccine include clinical trials conducted both in Korea and in other countries, WHO position papers, recommendations published by the U.S Centers for Disease Control and Prevention and the European Centre for Disease Prevention and Control. - Economic data: the cost, affordability, and financial sustainability of implementing the new vaccine program, vaccine's cost-effectiveness. - Recommendations by sub-committees and the KCDC: isolation of the patients, the prophylactic management among the patient's contacts, the diagnostic methods, the disease surveillance and the immunization.
Duclos et al., 2012	The framework considers guidance and recommendations from WHO adopting the GRADE approach.	- Epidemiologic features of the disease: disease burden (including age specific mortality, morbidity, and social impact), specifics risk groups, epidemic potential, disease occurrence over time (i.e., secular trends), serogroup or serotype distribution (for serogroup or serotype specific vaccines), changes in epidemiological features over time. - Clinical characteristics of the targeted disease: clinical management, disease severity and fatality, primary/secondary/tertiary care implications, long-term complications and medical care requirements. - Vaccine and immunization characteristics: efficacy, effectiveness and population impact of the vaccine (including herd immunity), safety, indirect effects, cold chain and logistical concerns, vaccine availability, vaccine schedule, social and programmatic acceptability of the schedule, ability to reach the target populations, ability to monitor programme impact.

		- Economic considerations: cost of illness, vaccine and vaccine delivery costs, potential for vaccine price reductions, cost-effectiveness of immunization programmes, affordability of immunization. - Health system considerations: possible interactions with other interventions and control strategies, possible impact of vaccine adoption on the wider health system. - Social impacts - Legal and Ethical considerations
Levine et al., 2010	This is proposed framework based on observations of the process and drivers of new vaccine adoption in Global Alliance for Vaccines and Immunization (GAVI) eligible countries. Considers guidance and recommendations from WHO.	*Establish and organize evidence:* - Epidemiology and burden of the disease (including the distribution of serotypes or strains if relevant to vaccine policies). - Evidence-based on the safety, efficacy and relative cost effectiveness of the vaccine as a solution. *Establish supportive global policies:* - Vaccine recommendations. - Financing policies - Procurement mechanism *Translate polices into local action:* - Political will to implement - System to deliver and monitor
Makinen et al., 2012	Principal factors considered in decision-making processes of new vaccine adoption in lower-middle-income countries (LMICs).	- Burden of disease data (e.g. Mortality and morbidity) - Cost related drivers: vaccine market information, cost-effectiveness, budget impact and affordability, and available financing. - Other decision-making factors: the experience of neighbouring countries, access to adequate procurement mechanisms and the role played by global/regional bodies to engage countries. - Recommendations include making epidemiological data and vaccine market information accessible to countries, building and reinforcing related analysis capacity, and promoting more efficient procurement mechanisms such as pooling.
Piatti 2011	The decision-making procedure is divided in five analytical steps. For each step are provided methods and indicators, one of them is the GRADE approach.	- Step 1) Safety: Adverse Events (nature and frequency); Risk factors and groups at risk; Biological effects (biological disequilibrium) of the vaccine. - Step 2) Medical-Socio-Sanitary Aspects: Burden of disease, including the social impact of the disease; Efficacy, Vaccine coverage. - Step 3) Cost-Efficacy Analysis: Direct and indirect cost, Modelling; Discounting; Vaccine effectiveness; Alternative scenario evaluation. - Step 4) Other implementation-related aspects: Legal aspects; Ethical aspects and Equity. - Step 5) Priority: Integration of the above mentioned points with the sense of urgency for introducing it.
Piso and Wild 2009	The decision-making procedure is divided in seven analytical steps.	- Step 1) Public health relevance and alternative measures, immunization strategy, conformity of programs, research questions. - Step 2) Disease considerations: burden of disease, clinical manifestations,

	Elements belonging to the first step were considered more important and incisive in shaping the decisional process than the following ones.	current treatment, epidemiology, risk groups and risk factors, social impact and other preventives measures; Vaccine considerations: vaccine characteristics, supply, administration schedule, immune response, efficacy and utilization, population effectiveness and safety. - Step 3) Cost-effectiveness analysis. - Step 4) Considerations on acceptability and feasibility of the new program, equity and ethical implications, legal and political considerations, potential side effects. - Step 5) Final decision: decision-making process itself. - Step 6) Implementation. - Step 7) Surveillance of vaccine coverage and utilization, of epidemiologic changes, the frequency and nature of adverse events, immune surveillance and re-evaluation (revision).
Tapia-Conyer et al.	The evidence-basis of the Commission for the Future of Vaccines in Latin America (COFVAL) and feasibility.	- Burden of disease and vaccine coverage - Epidemiological surveillance - National health accounts - Regional vaccination reference schemes - Professionalising immunisation policies and practices - Vaccine Advisory Committees - Innovative financing mechanisms for purchasing vaccines

We then quantified the frequencies of each dimension considered across the conceptual frameworks analysed (Appendix 4, Additional file 4). The most common dimensions were: *Importance of illness or problem, Vaccine characteristics, Resource use, Decision-making* and *Feasibility.*

Formerly, we extracted the criteria reported in the frameworks and we organized them into the ten dimensions identified, in order to quantify their frequencies (Appendix 4, Additional file 5). The most common information report in all frameworks was *Health economic analyses*. Information about *Vaccine efficacy and effectiveness* and *Vaccine safety*, from the dimension *Vaccine characteristics (benefits and harms)* were reported in almost all the frameworks. Then, in the dimension of *Importance of illness or problem* the most reported were *Incidence*, *Prevalence*, *Mortality*, *Social impact* and *Specific risk groups.*

Regarding a methodologically rigorous system used in the frameworks the studies of Ahmed et al., Duclos et al., Piatti and Tapia-Conyer et al., proposed the use of GRADE approach [40] for the information about the vaccine effectiveness and safety. In the study of Piatti and Blecher et al., it was indicated how to obtain the data of each dimension of the framework. For example, in the study of Blecher et al., in their dimension named *Burden of disease*, the

information comes from the data reported by the National Department of Health; in their dimension named *Effectiveness of the vaccine* the information comes from published studies in reputable international journal, if possible meta-analysis or Cochrane reviews (see Table 3.5.1).

Eight of the frameworks reported that they considered guidance and recommendations from WHO guidelines.

After carefully reviewing the frequency, their hierarchy, the reciprocal relationship and the standardization of terminologies of the ten dimensions reported, as well as the methods used in the frameworks, we proceeded to link the ten dimensions of the considered studied to the ones of the general EtD framework, grouping some dimensions together. In some case, such as *Importance of illness or problem*, *vaccine characteristics and impact of the immunisation programme,* and *resource use,* the dimensions were consistently repeated across the frameworks, although the exact terms used to describe each dimension might have varied. For instance, the exact terms used to describe *Importance of illness or problem* might have varied and included *burden of illness, seriousness of the problem, number of people affected*; the terms *vaccine benefits and harms, impact of vaccination or immunisation programmes*, were used interchangeably with, arguably, the same meaning as *vaccine characteristics*. These terms were indeed grouped under the umbrella of the dimension named *vaccine characteristics and impact of the immunisation programme*. In other cases, the extend of the overlap between frameworks and the EtD framework was less straightforward. For instance, *Acceptability, Legal and political considerations* and *Decision-making* were placed under the umbrella of *Feasibility*. Thus, we might have interpreted and altered the original constructs as presented in the original papers.

Table 3.5.2 presents the EtD six dimensions adapted to the vaccine context. The dimensions are represented by: *Burden of disease, Vaccine characteristics and impact of immunisation programme, Values and preferences, Resource use, Equity* and *Feasibility*. Each dimension is provided by a brief description and the related information.

Table 3.5.2: Proposed conceptual framework to support vaccine adoption

DIMENSIONS	DESCRIPTION	QUESTIONS	INFORMATION
Burden of disease	Description of epidemiology, clinical features and sequelae of the disease/condition in terms of public health consequences.	Is the disease/condition severe? Is the disease/condition frequent? Is the vaccination a priority?	- Frequency of the disease/condition (e.g., incidence, prevalence, secular trends). - Severity of the disease/condition (e.g., mortality, morbidity). - Social impact of the disease/condition (e.g., hospitalisation rate, sickness absenteeism, high-risk groups, clinical features, perception of importance, other preventive measures)
Vaccine characteristics and impact of immunisation programme	Description of the effects and adverse events of the vaccine; using the GRADE method. Overall quality of the available evidence of effects across all of the outcomes, which are critical to making a decision.	Are the desirable anticipated effects large? Are the undesirable anticipated effects small? What is the net benefit of the vaccination? What is the overall certainty of this evidence (e.g., how confident we are about the net benefit of the vaccination)?	- Vaccine characteristics or properties (e.g., components, types, target population, posology). - Efficacy (e.g., immunogenicity, strain coverage, capacity to reduce the disease incidence, capacity to disrupt carriage, duration of protection, serotype replacements). - Safety (e.g., reactogenicity, adverse events, interaction with other vaccines)
Values and preferences	Consideration of values and preferences of patients/care givers about the balance between desirable and undesirable effects of the vaccine.	How certain is the relative importance of the desirable and undesirable outcomes? Would patients/caregivers feel that the benefits outweigh the harms and burden? What is the appreciation and value of the vaccination in the population?	- Values and preferences of citizens about the balance between desirable and undesirable effects of the vaccine. - Perspectives and perceptions of the citizens and health professionals about the disease and the vaccine.
Resource use	All the information about costs, use of resources and health outcomes gained.	Is the incremental cost small relative to the net benefits? Is the total cost (impact on budget) small? What are the costs of the vaccination and are they limited compared to the benefits?	- Vaccination costs (e.g., costs of the vaccine, administration costs, costs arising from potential adverse effects). - Budget impact and financial sustainability. - Health economic analyses (e.g., cost-effectiveness analysis, cost-benefit analysis, cost-utility analysis) - Direct and indirect costs.
Equity	Impact on health inequities and ethical considerations.	What would be the impact on health inequities? Would some part of the population taking advantage from the vaccination compared to other groups?	- Ethical considerations - Equity (e.g., accessibility; equal distribution of resources, benefits risks, costs, etc. related to the vaccination programme).
Feasibility	Information on applicability and possible barriers, acceptability,	Is the option feasible to adoption in the actual setting?	- Acceptability of the vaccination among the population and health care professionals.

	organisational impact, alternative scenarios, control system.	Which vaccination barriers or facilitators act at the system level?	- Feasibility of the implementation of the programme (e.g., vaccination coverage, ability to reach the population target, vaccine availability and supply, recommendation). - Alternative interventions (e.g., effectiveness and cost-effectiveness of alternatives). - Surveillance system.

3.5.3 Discussion

This review analysed the existing frameworks addressing the adoption of new vaccines in order to identify their most critical, accepted and comprehensive components for decision makers. The dimensions proposed across frameworks aim to inform and support coverage decisions (e.g. decisions by third party payers about whether and how much to pay for vaccines). The taxonomy used to refer to dimensions across different frameworks had a sufficient level of similarity to aggregate dimensions under umbrella terms. Overall, *Burden of disease, Vaccine characteristics, Resource use, Decision-making and Feasibility* were frequently reported across frameworks as the key factors to consider in vaccine adoption decision-making, while *Values and preferences* and *Acceptability* were less consistently reported.

We considered that many of the dimensions presented in the included SRs and primary studies were broad and lacking practical details for effective application in the evaluation or in the comparison of vaccine strategies to guide vaccine adoption decision-making. The benefit and safety of vaccines, for example, were only slightly addressed. At the same time most frameworks were generally qualitative: they did not report key issues, such as the study designs to privilege, how to assess the risk of bias, how to analyse benefits and risks (e.g., which relative and absolute measures to use), the value to award patient reported outcome measures and the minimal important differences.

Limitations

The main limitation is that we did not appraise the included frameworks for quality. Thus, some of the conclusions of this review may come from studies that are susceptible to bias. A second limitation is that we focused on vaccine frameworks. If vaccines are not different from other interventions, particularly drugs, a systematic review with a broader perspective might have added other relevant elements. Indeed our work serves as a starting point to define and

develop a usable framework to inform vaccine coverage decisions, recognizing however the future need to address the above conceptual and methodological issues and to increase also its broader applicability.

The structure of the DECIDE EtD framework could be useful in conceptualising all relevant dimensions and facilitating consistent use of appropriate criteria and transparent use of evidence.

Note: The development of this review was supported by the Lombardia Region.

An article reporting the results of the review was recently published (Gonzalez et al. Vaccine Decision Group. Conceptual frameworks and key dimensions to support coverage decisions for vaccines. Vaccine. 2014 Dec 19).

Chapter 4: Description of the conceptual framework

Creating good ideas is easy, but choosing among them is hard.

Jonathan Rosenberg
(Think Quarterly Google, December 2012)

The general structure of the EtD framework is common to all DECIDE' WPs and tailored for different target audiences (eg. clinicians, policy makers, guidelines' developers, patients, etc…) [7]. It was developed using the methodologies described in Chapter 3.

The EtD is intended to:

- Inform about the pros and cons of each option (intervention) that is considered
- Ensure that important factors that determine a decision(criteria) are considered
- Provide a concise summary of the best available research evidence to inform judgements about each criterion
- Help structure discussion and identify reasons for disagreements
- Make the basis for decisions transparent

The last version of the EtD for coverage includes 12 criteria deemed as essential for taking this type of decision.

In Table 4.1 are listed all the criteria included in the framework with a brief description of which type of information are provided for each of them.

In Appendix 5 a series of practical examples of application of the EtD to specific questions are available (from the more recent version to the oldest one). The examples provide an overview of the evolution of the structure of the framework over time starting from the most recent one.

Table 4.1. Criteria of the EtD Framework for Coverage

Domains	Criteria	Description	Type of Information
Problem	Is the problem a priority?	The more serious a problem is, the more likely it is that an option that addresses the problem should be a priority.	- Severity of the disease/condition - Frequency of the disease/condition - Social impact of the disease/condition
Benefits & harms	How substantial are the desirable anticipated effects? How substantial are the undesirable anticipated effects?	The larger the benefit, the more likely it is that an option should be covered. The greater the risk of undesirable effects, the less likely it is that an option should be covered.	- Efficacy and safety data on critical outcomes (those that are driving a decision) - Evaluation of the quality of evidence for each outcome according to the GRADE method
Certainty	What is the overall certainty of the evidence of effect?	What is the overall certainty of the evidence of effects across all of the outcomes that are critical to take a decision? The less certain the evidence is for critical outcomes, the less likely that an option should be covered (or the more important it is likely to be to conduct a pilot study or impact evaluation, if it is covered).	- Overall quality of evidence across critical outcomes according to the GRADE method
Values	Is there important uncertainty about how much people value the main outcomes?	The more likely it is that different assumptions in values would lead to different decisions; the more important it is to obtain evidence of the values of those affected. Values in this context refer to the relative importance of the outcomes of interest (how much people value each of those outcomes).	- Values and preferences of citizens about the balance between desirable and undesirable effects of the intervention. - Perspectives and perceptions of the citizens about the disease and the intervention.
Balance	Does the balance between desirable and undesirable effects favour the intervention or the comparison?		-
Resource use	How large are the resource requirements (costs)? What is the	Big costs per unit of benefit may represent a problem of coverage.	- Budget impact and financial sustainability. - Direct and indirect costs. - Health economic analyses

	certainty of the evidence of resource requirements? Does the cost-effectiveness of the intervention favour the intervention or the comparison?		
Equity	What would be the impact on health equity?	Policies or programs that reduce inequities are more likely to be a priority than ones that do not (or ones that increase inequities).	- Ethical considerations - Equity (e.g., accessibility, gender equity, equal distribution of resources)
Acceptability	Is the option acceptable to key stakeholders?	The less acceptable an option is to key stakeholders, the less likely it is that it should be covered, or if it is covered, the more likely it is that an implementation strategy to address concerns about acceptability should be included.	- Professionals' acceptability - Patients and caregivers' acceptability
Feasibility	Is the option feasible to implement?	The less feasible (capable of being accomplished or brought about) an option is, the less likely it is that it should be covered (i.e. the more barriers there are that would be difficult to overcome).	- Applicability and possible barriers - Organisational impact

4.1 Main features

The EtD includes a structured PICOS (Patient/Intervention/Comparison/Outcome/Setting) question about the coverage decision to be taken, a concise summary with all the background information needed and a *table* with the following columns:

- *Domains:* factors that should be considered for coverage decisions
- *Criteria*: specific aspects of each domain that are particularly important for taking coverage decisions
- *Judgements:* considerations that must be made in relation to each criterion taking into account the evidence available, which may include draft judgements suggested by the people who have prepared the framework
- *Research Evidence:* information about the research evidence available relevant for the decision which may include links to more detailed summaries

- *Additional considerations:* any additional information, not "research evidence" or comments by the people who have prepared the framework that can be useful to justify or better understand the judgement

The final section of the EtD is designed to help the stakeholder in summarising the information reported above and taking the decision and consists of:

- *Decision* (to cover, not to cover or coverage with evidence development)
- *Justification* for the decision, flowing from the judgements in relation to the criteria
- *Restriction*, if any, to the adoption of the option/intervention
- *Implementation considerations,* if any, including strategies to address any concerns about the acceptability and feasibility of the option
- *Monitoring and evaluation considerations,* if the intervention (option) is implemented, including any important indicators that should be monitored and any needs for further evaluation

EtD frameworks should be prepared by multidisciplinary technical teams with expertise in understanding of systematic review methods for effects, the GRADE system, the specific topic of the decisions and also an understanding of systematic review methods for qualitative research and economic analysis.

In general research evidence derived from systematic reviews or single studies should be used to inform judgements about each criteria. The source of the evidence summarised in the framework should be referenced and any limitations of how the evidence was summarised should be noted, particularly when the source is not a systematic review.

If it is not possible to find any research evidence for one or more criteria, any relevant information or assumptions useful to make a judgement should be included under additional considerations.

4.2 Domains and criteria

Problem: Is the problem a priority?

The more serious a problem is , the more likely is that an intervention that adresses the problem should be a priority. Information relevant for this criteria are: severity (e.g., mortality, morbidity), frequency (e.g., incidence, prevalence) and social impact of the disease (e.g., hospitalisation rate, sickness absenteeism, high-risk groups, clinical features, perception of importance, other preventive measures). It is also important to provide information that are relevant for the setting the decision should be applied to, for this reason data coming from local/regional/national registries or current data collected ad hoc represents a useful source for this criteria.

Benefits & Harms: How substantial are the desirable anticipated effects? How substantial are the undesirable anticipated effects?

The more substantial the desirable effects in relation to the comparison, the more likely it is that an intervention (option) should be covered and equally the more substantial the undesirable effects (harms and burden) in relation to the comparison, the less likely it is that an intervention (option) should be covered.

Information provided for this criteria are: efficacy and safety data on critical outcomes (those that are driving a decision) and evaluation of the quality of evidence for each outcome according to the GRADE method. This information is reported in the EtD using a Summary of Findings (SoF) table format as the one shown in Figure 4.2.1 [18, 41, 42].

A SoF table presents the main findings of a systematic review (if a systematic review is not available it could also be used to summarise single studies) in a transparent and simple tabular format. In particular, key information is provided concerning number of studies and patients included, the magnitude of effect of the interventions examined, the sum of available data on the main outcomes and the certainty of evidence for each outcome considered. Footnotes about the evaluation of the quality of evidence are also provided.

The certainty of the evidence is a judgement about the extent to which we can be confident that the estimates of effect are correct. These judgements are made using the GRADE system, and are provided for each outcome. The judgements are based on the type of study design (randomised trials versus observational studies), the risk of bias, the consistency of the

results across studies, and the precision of the overall estimate across studies. For each outcome, the certainty of the evidence is rated as high, moderate, low or very low [19]. A summary of the GRADE approach to rating the certainty of the evidence is shown in Figure 4.2.2.

Figure 4.2.1: An example of SoF table for EtD

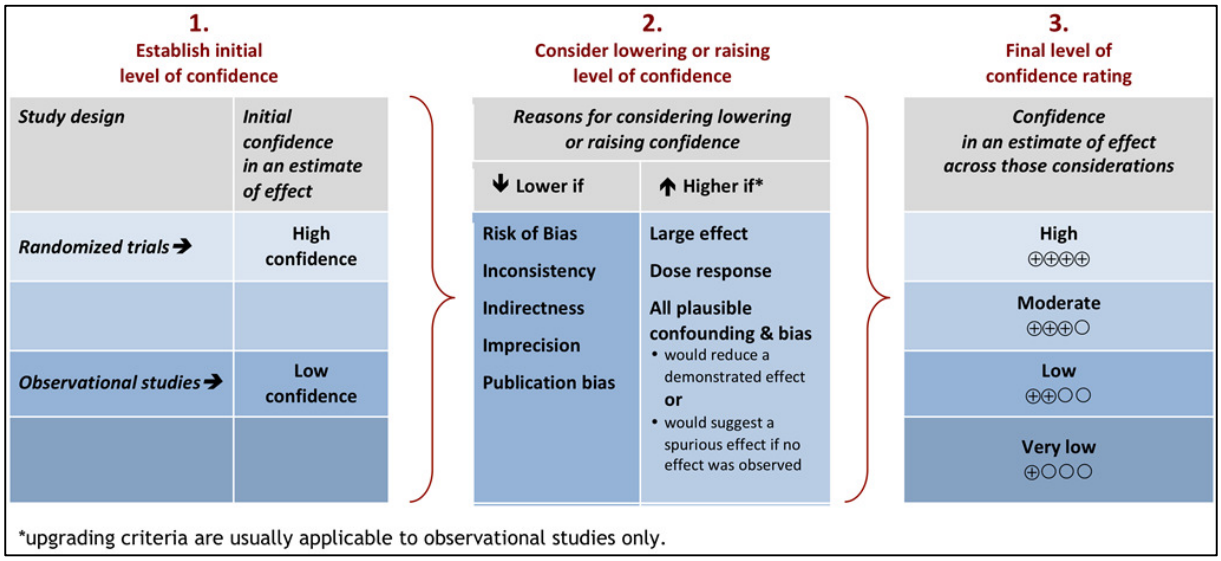
Summary of findings: *Screening vs no screening (Cochrane 2013)*

Outcome[1]	Control	Screening	Relative effect (RR) (95%CI)	Certainty of the evidence (GRADE)
All-cause mortality (294856 pts in 4 studies)	21 per 100	21 per 100 (20 to 22)	**RR 1** (0.96 to 1.03)	⨁⨁⨁◯ Moderate[2]
Prostate cancer specific mortality (341342 pts in 5 studies)	7 per 1000	7 per 1000 (6 to 8)	**RR 1** (0.86 to 1.17)	⨁⨁⨁◯ Moderate[3]
Prostate cancer diagnosis (294856 pts in 4 studies)	68 per 1000	88 per 1000 (69 to 112)	**RR 1.3 (1.02 to 1.65)**	⨁⨁◯◯ Low[2,4]

[1] Information on costs, quality of life, metastatic disease at follow up, and harms of screening was limited and could not be meta-analysed;
[2] Risk of bias was 'high' or 'unclear' for allocation concealment in 3 studies; 'high' or 'unclear' for random sequence generation in 2 studies; 'low' for blinding in all 4 studies; ' unclear' for incomplete outcome data in 2 studies; 'unclear' for selective reporting in 1 study;
and 'high' or 'unclear' for other bias in 2 studies.
[3] Risk of bias was 'high' or 'unclear' for allocation concealment in 4 studies; 'high' or 'unclear' for random sequence generation in 3 studies; 'unclear' for blinding of outcome assessment in 1 study; 'unclear' for incomplete outcome data in 2 studies; 'unclear' for selective reporting in 2 studies; and 'high' or 'unclear' for other bias in 3 studies.
[4] I2 = 98%; Chi2 = 162.78 (P <0.00001).

Judgements about how substantial effects are must take into account the absolute effect (the difference between the proportion of people who would benefit, or the amount they would improve, from the intervention and the proportion of people who would benefit, or the amount they would improve from the comparison) and the importance of the outcome (how much it is valued).

Figure 4.2.2: Grade approach to rating the certainty of the evidence



Courtesy of the GRADE Working Group

Certainty: What is the overall certainty of evidence of effect?

The less certain the evidence is for the main outcomes, the less likely it is that an intervention should be covered or prioritized, and the more likely it is that it should be evaluated.

The overall certainty (or quality) of evidence is an assessment of how good an indication the research provides of the likely effect; i.e. the likelihood that the effect will be substantially different from what the research found. "Substantially different" means a large enough difference that it might affect a decision. This assessment is based on an overall assessment of all the critical outcome(those that are driving a decision) and refers to the lowest certainty for any of the critical outcomes according to the GRADE system [43]. The GRADE system uses four categories of certainty shown in Table 4.2.1.

Table 4.21: Categories for certainty of the evidence

Ratings	Definitions
⊕⊕⊕⊕ High	This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low.
⊕⊕⊕◯ Moderate	This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different* is moderate.
⊕⊕◯◯ Low	This research provides some indication of the likely effect. However, the likelihood that it will be substantially different* is high.
⊕◯◯◯ Very low	This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different* is very high.

* Substantially different = a large enough difference that it might affect a decision

Values: Is there important uncertainty about how much people value the main outcomes?
Uncertainty about how much those affected value the outcomes of interest can lead to different decisions about coverage.

People value their health (eg. being in good health more than being in pain, having other symptoms or being disabled). One way of expressing the value of a health state is to use utility values, a measure the strength of the preference people have for a specific health state, from 0 (for death) to 1 (for perfect health). For example, a severe stroke might have a utility value of 0.10, a minor stroke might have a utility value of 0.75 and a serious gastrointestinal bleed a utility value of 0.90. This indicates that the relative importance of a severe stroke (or how much people value avoiding a severe stroke) is more than that of a minor stroke, which is more than that of a gastrointestinal bleed.

Research evidence of how much people value the outcomes of interest can come from studies that have measured utility values or, ideally, from systematic reviews of those studies. Utility values can be measured using different techniques (e.g. using a standard gamble, time trade off or visual analogue scale) and how they are measured can affect the values, including the technique that is used, how the health states are described and who the respondents are.

Evidence of how much people value the outcomes of interest might also come from studies that directly measure the choices people make when presented the probabilities of the desirable and undesirable effects, a description of those outcomes (health states) and information about when they would occur and how long they would last. Also qualitative research evidence could be a good source of information for this criteria.

Empirical evidence about people values and preferences is often lacking or not exhaustive so it is usually complemented by information coming from editorials, anecdotes and consultation with patients and experts of the field. These information should be reported and detailed in the "additional considerations" section.

Balance: Does the balance between desirable and undesirable effects favour the intervention or the comparison?

Judgements about the balance of the desirable and undesirable effects need to take into account:

- How substantial the desirable and undesirable effects are, and the certainty of the evidence of effects
- How much the people affected value the main outcomes, and uncertainty about or variability in those values

The evidence and additional considerations that inform judgements about the balance between the desirable and undesirable effects includes the evidence and additional considerations that were summarised for the four preceding criteria (Benefit and harms, Certainty, Values). Although this criterion subsumes those criteria, they can have an independent effect on a decision beyond this, and therefore are included separately. For example, a panel may be more likely to decide to cover an intervention that is lifesaving than another intervention with similar net benefits but less substantial desirable effects.

Resource use: How large are the resource requirements (costs)? What is the certainty of the evidence of resource requirements? Does the cost-effectiveness of the intervention favour the intervention or the comparison?

The greater the cost, the less likely it is that an intervention (option) should be a priority. Conversely, the greater the savings, the more likely it is that an intervention (option) should be a priority.

This criteria refers to the overall resources that the organization will use for the new intervention, measuring changes in the budget of the organization and includes information about budget impact, financial sustainability, direct and indirect costs. All these information should be contextualised, so they should retrieved specifically for each decision depending on the setting under consideration.

The less certain the evidence is for resource requirements, the less likely it is that an intervention should be covered. Judgements about the certainty of the evidence for resource requirements are similar to judgements about the evidence of effects [44]. This requires finding evidence for the differences in resource use, making judgements regarding confidence in effect estimates using the same criteria used for health outcomes, and valuing the resource use in terms of costs for the specific setting for which decisions are being made. Evidence for resource use may come from the same studies that are included in a systematic review of effects. Additional sources of evidence include observational studies (that may or may not be included in a systematic review of effects), technology appraisals, and economic evaluations. Evidence for resource use in a specific setting may be also retrieved from national or local databases, such as drug use from prescription databases or hospitalizations from hospital databases.

The greater the cost in relation to the net benefit, the less likely it is that an intervention should be recommended. Judgements about the cost-effectiveness of an intervention need to take into account several factors, including:

- The balance between the desirable and undesirable effects (the net benefit), the certainty of the evidence of effects, and uncertainty about or variability in how much people value the main outcomes
- Resource requirements (costs) and uncertainty about the costs

The evidence and additional considerations that inform judgements about the cost effectiveness of interventions (options) includes the evidence and additional considerations that were summarised for the six preceding criteria. Although this criterion subsumes those criteria, they can have an independent effect on a decision or recommendation beyond this. For example, a panel may be more likely to recommend or decide to recommend or cover some interventions (options) with a relatively high cost-effectiveness ratio and not others

with a similar cost effectiveness ratio but less substantial desirable effects, a substantially smaller net benefit or more uncertainty about its effects [9].

Equity: What would be the impact on health equity?

Interventions that reduce inequities are more likely to be a priority than ones that do not (or ones that increase inequities). Potential impacts on equity could be considered examining the effects of an intervention and its possible differential effects on disadvantaged populations. Factors to be taken into account might include: economic status, employment or occupation, education, place of residence, gender or ethnicity, accessibility. Also for this criteria information derived from empirical evidence are difficult to find.

The following questions can help to guide considerations of the potential impacts on equity [45-47]:

- Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention (option) for disadvantaged groups or settings?
- Are there different baseline conditions across groups or settings, such that the absolute effectiveness of the option would be different, or the problem would be more or less important, for disadvantaged groups or settings?
- Are there important considerations that should be made when implementing the option in order to ensure that inequities are reduced, if possible, and that they are not increased?

Acceptability: Is the option acceptable for key stakeholders?

The less acceptable an intervention is to key stakeholders, the less likely it is that it should be covered, or if it is covered, the more likely it is that an implementation strategy might be needed to address concerns about acceptability. Acceptability has to do with the willingness of the stakeholders (patients and professionals) to accept the introduction of an intervention and it involves moral values, preferences, professional believes, etc…

An intervention might be unacceptable due to the distribution of the benefits, harms and costs: for example, people who would have increased costs or burdens without experiencing the benefits of an intervention (option), might find this unacceptable.

Feasibility: Is the option feasible to implement?

The less feasible (capable of being accomplished or brought about) an intervention is, the less likely it is that it should be covered. Information useful for this criteria refers to applicability, possible barriers and organisational impact [48]. Considerations about these factors could be incorporated directly into the decision addressing key barriers to implementing it in conclusive part of the EtD.

Also this criteria, like acceptability, is difficult to be informed because empirical evidence is almost always lacking. Moreover it is strongly linked to local context so information about it should be tailored ad hoc.

4.3 Taking the decision

The EtD framework for coverage decisions includes five options for coverage decisions:

- no coverage
- coverage with evidence development
- coverage with price negotiation
- restricted coverage
- full coverage

One or more of the criteria used to assess interventions can drive decisions about coverage and this can vary from decision to decision.

A decision to cover an intervention in the context of research (with evidence development) can be made when there is important uncertainty about the effects of an intervention. Although this is an attractive option for new, promising interventions, it could be difficult to implement [49, 50]. Coverage with price negotiation is common for new, effective drugs that do not meet standards for resource use or cost effectiveness. Restricted coverage is also commonly used for interventions that are only beneficial or cost-effective for a subgroup of patients.

For coverage decisions it may be particularly important to monitor usage, inappropriate usage and costs. When inappropriate use is a concern, it may be possible to monitor this using

registries or other routinely collected data. However, this requires that reliable data are collected that make it possible to distinguish between appropriate and inappropriate use.

4.4 Discussion

The main strengths of the EtD framework for coverage decisions are its design and structure, summarising in a logical and transparent way all the elements of a complex decision-making process. The EtD framework guides consideration of the important factors that should determine a decision about coverage, and can helps to avoid potential inappropriate influences. The application of a structured and transparent approach to coverage decisions was perceived as a strong point in favour of using the EtD framework, and its innovative nature was particularly appreciated by participants in user testing an pilot tests.

From the perspective of clinicians and patients affected by coverage decisions, use of the EtD framework can help to ensure that decisions are fair. It is a clear document that helps to ensure consistent use of appropriate criteria for assessing interventions and transparent use of evidence to inform judgements for each criterion. It can facilitate identification of reasons for disagreements and feedback on a draft decision prior to making a final one.

The main weakness is the usability of the framework by stakeholders with different levels of methodological knowledge. However, it might also be considered a potentially useful instrument to facilitate better understanding of the methodological considerations that are inherent in evidence-based coverage decisions.

The criteria that are used to assess interventions in the EtD framework for coverage decisions are not new. They are similar to criteria already used by many organisations and to the criteria suggested by the GRADE Working Group for clinical recommendations. However, the structure of the EtD framework, linking criteria to explicit judgments and to the evidence available to inform each of them is innovative. The framework offers a way for organisations to monitor their decisions, and it can facilitate sharing, comparing and learning across organisations.

A complete description of the main characteristics of the EtD frameworks developed for various target audiences (not only the coverage one) has been prepared by the DECIDE group and will be available as a guide for preparation and use of the EtD in different context.

4.5 Dissemination activities

One of the objective of the DECIDE Project is to try to disseminate the strategies developed in order to incentive their application in the real world of decision-making processes.

Below a description of the dissemination activities of WP2 at this point.

4.5.1 Workshops

We organised several national and international workshops. They had an interactive format and were structured with a brief introduction to the DECIDE Project, a short presentation of the conceptual framework applied to a practical example and a group session during which we asked participants to mimic the process of taking a coverage decision using the framework provided.

List of the workshops organised:

1. "Dalle evidenze alle decisioni per il sistema sanitario nazionale: il Progetto DECIDE" Davoli M, **Parmelli E**, Saitto C. 7° Congresso Nazionale Società Italiana di HTA, Rome 27 Seeptember 2014.
2. "Using a conceptual framework to go from evidence to decisions of disinvestment" **Parmelli E**, D'Amico R, Davoli M. Developing and Evaluating Communication strategies to support Informed Decisions and practice based on Evidence. International Conference: Better clinical guidelines, better healthcare decisions. Edinburgh (UK), 2-4 June 2014.
3. "Dalle evidenze alle decisioni per il sistema sanitario nazionale: il Progetto DECIDE" Amato L, Davoli M, Di Martino V, **Parmelli E**, Panico S. Annual Meeting Associazione Alessandro Liberati – Network Italiano Cochrane, Naples 13 December 2013.
4. "Going from evidence to dis-coverage decisions" Davoli M, **Parmelli E**, D'Amico R, Amato L. XXI Cochrane Colloquium, Quebec City, Canada 19-23 September 2013.

5. “Se una notte d’inverno un decisore... Con DECIDE, dalle evidenze alle decisioni nel SSN” Amato L, Davoli M, Magrini N, Oxman A, **Parmelli E**, Pregno S, Saitto C, Schunemann H. Rome, 1 March 2013.
6. “Going from evidence to coverage decisions” Liberati A, Oxman A, **Parmelli E**. XIX Cochrane Colloquium, Madri, Spain 19-22 October 2011.

4.5.2 Presentations and posters at national and international conferences

1. “Developing a conceptual framework for going from evidence to coverage decisions” Parmelli E, Amato L, Davoli M. Evidence Live 15, University of Oxford (UK) 13-14 April 2015. (Oral presentation – Accepted)
2. “Come comunicare le conoscenze scientifiche utili per supportare decisioni di pratica e politica sanitaria” **Parmelli E**, Amato L, Brunetti M, Magrini N, Nonino F, Pregno S, Saitto C, Davoli M. Annual Meeting Associazione Alessandro Liberati – Network Italiano Cochrane, Milan 23 May 2014. (Poster)
3. ”Quali evidenze sono utili per prendere decisioni di politica sanitaria: il progetto DECIDE” **E Parmelli**. XXXVII Congresso dell’Associazione Italiana di Epidemiologia, Rome, 4-6 November 2013. (Oral presentation)
4. “The DECIDE Project: Policy Makers and Managers focused strategies to go from Evidence to Coverage Decision” Davoli M, Pregno S, **Parmelli E**, Amato L, Brunetti M, De Palma R, Magrini N, Nonino F, Saitto C. XX Cochrane Colloquium, Auckland (New Zeland) 30 September- 3 October 2012. (Poster)

4.5.3 Publications

1. González-Lorenzo M, Piatti A, Coppola L, Gramegna M, Demicheli V, Melegaro A, Tirani M, **Parmelli E**, Auxilia F, Moja L; the Vaccine Decision Group. Conceptual frameworks and key dimensions to support coverage decisions for vaccines. Vaccine. 2014 Dec 19.
2. **Parmelli E**, Amato L, Saitto C, Davoli M; Gruppo di Lavoro "DECIDE Italia. DECIDE: developing and evaluating communication strategies to support informed decisions and practice based on evidence. Recenti Prog Med. 2013 Oct;104(10):522-31.

3. Treweek S, Oxman AD, Alderson P, Bossuyt PM, Brandt L, Brożek J, Davoli M, Flottorp S, Harbour R, Hill S, Liberati A, Liira H, Schünemann HJ, Rosenbaum S, Thornton J, Vandvik PO, Alonso-Coello P; DECIDE Consortium (**Parmelli E**). Developing and Evaluating Communication Strategies to Support Informed Decisions and Practice Based on Evidence (DECIDE): protocol and preliminary results. Implement Sci. 2013 Jan 9;8:6.

4.6 Future developments

Development of an interactive format of the EtD

As already mentioned in the previous chapters, WP5 of the DECIDE Project is developing an interactive format of the EtD framework (iEtD). The prototype has already been tested and revised by WP5 and we are ready to test it on WP2's stakeholders.

The iEtD have a flexible format enabling users/organisations to tailor the framework, reports and interactive resources to help target audiences to go from evidence to a decision. Organisations will be able to modify the terminology, explanations, criteria and response options. They will also be able to generate tailored interim reports (e.g. to consult decision makers or stakeholders) and final reports (e.g. tables or appendices to a recommendation or decision).

Evaluation of the EtD in comparative studies

To solve problems of usability emerged during the stakeholders' consultation and the user testing, different formulation of the information related to specific criteria will be prepared and compared within formal studies to find the best presentation for our target audience.

Piloting the EtD with real decisions

The EtD framework will be pilot tested on real decisions.

We already had contact with regional commissions (e.g. Lombardia vaccines' commission, Lezio and Emilia Romagna drugs' commissions) and we will ask them to pilot the EtD on coverage decisions they have to make in the future.

Also WHO gave is availability to pilot test the EtD in specific groups (e.g. Essential medicine list).

Pilot testing will give us the possibility of collecting comments and suggestion and further refining the EtD to prepare it for the real world of decision-making process.

References

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Appendices

Appendix 1: Survey

Survey questionnaire

Appendix 2: Stakeholders' feedbacks

Feedback questionnaire

Appendix 3: User testing

Interview guide

Appendix 4: Systematic review of vaccines' frameworks

Additional file 1: excluded studies

Additional file 2: Dimensions considered across frameworks

Additional file 3: Information considered across frameworks

Appendix 5: Evolution of the EtD framework over time

Appendix 1: Survey

Survey of policymakers and managers regarding going from evidence to coverage decisions

DECIDE (www.decide-collaboration.eu) is a collaborative research project funded by the European Commission's Seventh Framework Programme. The project's objective is to develop and evaluate communication strategies to support evidence-informed decisions by building on the work of the GRADE Working Group (www.gradeworkinggroup.org) and the Cochrane Applicability and Recommendations Methods Group (www.armg.cochrane.org). As part of this project we are developing specific tools to assist policymakers responsible for coverage decisions. The purpose of this survey of a diverse sample of policymakers and managers is to explore their perceptions regarding current practices. In particular, we want to obtain input regarding a framework for going from evidence to coverage decisions.

Methods

The sampling frame will include policymakers, managers and their support staff in each of 8 partner country who have responsibility for coverage decisions. By coverage decisions we mean "decisions by third party payers -public or private health insurers- about whether and how much to pay for interventions (including drugs, tests, devices and services) and under what conditions".

Participants will be contacted by email and asked to complete the survey online. Initial contacts will be made by our partners in each country in the language of the participants. Non-responders will receive reminders after two and four weeks. The results will be reported using frequencies and percentages. Our primary analysis will focus on implications for the strategies that we are developing. No statistical analyses are planned. However, in secondary analyses we will explore potential differences in responses across participants from different countries and across groups with different types of experience.

1) Institution of membership:

Institute / National Agency

Institute / Regional Agency

University/ Hospital

Public Hospital/Clinic

Private Hospital/Clinic

NGOs

Other (specify)

2) Position held (you can specify more than one role):

3) Type of training:

Medical

Psychological/Social

Legal

Administrative

Economic

Other (specify)

4) Please describe the last three recent coverage decisions (decisions by third party payers -public or private health insurers- about whether and how much to pay for drugs, tests, devices or services and under what conditions) that you were involved in:

1

2

3

(Note: If in question 2 you indicated more than one role, please specify the role you had when taking the listed decisions)

5) For the 3 decisions you listed, were each of the following criteria considered?

Criteria	Question	Decision 1	Decision 2	Decision 3	Comments
Severity	Are the consequences of the disease or condition severe or important?	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	
Benefits	Overall, are the desirable effects large?	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	
Harms	Overall, are the undesirable effects small?	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	
Quality of evidence	Overall, what is the certainty of the anticipated effects (in our setting)?	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	
Value	Would patients/caregiver feel that the benefits outweigh the harms?	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	
Feasibility	Is the option feasible to adoption in the actual setting?	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	
Equity	Would the intervention reduce health inequities?	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	
Cost-effectiveness	Is the cost small relative to the net benefits?	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	

Criteria	Question	Decision 1	Decision 2	Decision 3	Comments
Budget	Is the total cost (impact on budget) low?	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	Yes ☐ Uncertain ☐ No ☐	

6) How important would you say it is to consider each of the following criteria when making coverage decisions? And how would they impact on them?

Criteria	Importance					Impact on coverage decision					Comments
Severity						**If the problem is serious you would choose to:**					
	Important ☐	Probably important ☐	Not sure ☐	Probably not important ☐	Not important ☐	Cover ☐	More probably cover ☐	Not relevant ☐	Less probably cover ☐	Not cover ☐	
Benefits						**If the benefits are large you would choose to:**					
	Important ☐	Probably important ☐	Not sure ☐	Probably not important ☐	Not important ☐	Cover ☐	More probably cover ☐	Not relevant ☐	Less probably cover ☐	Not cover ☐	
Harms						**If the risk of undesirable effects is small you would choose to:**					
	Important ☐	Probably important ☐	Not sure ☐	Probably not important ☐	Not important ☐	Cover ☐	More probably cover ☐	Not relevant ☐	Less probably cover ☐	Not cover ☐	
Quality of evidence						**If the overall certainty of the evidence of effects, across all of the outcomes that are critical to making a decision is high or moderate you would choose to:**					
	Important ☐	Probably important ☐	Not sure ☐	Probably not important ☐	Not important ☐	Cover ☐	More probably cover ☐	Not relevant ☐	Less probably cover ☐	Not cover ☐	

Value	Important ☐	Probably important ☐	Not sure ☐	Probably not important ☐	Not important ☐	**If desirable effects are large relative to the undesirable effects (patients/caregiver point of view) you would choose to:** Cover ☐	More probably cover ☐	Not relevant ☐	Less probably cover ☐	Not cover ☐
Feasibility	Important ☐	Probably important ☐	Not sure ☐	Probably not important ☐	Not important ☐	**If the option is feasible to adoption in the actual setting you would choose to:** Cover ☐	More probably cover ☐	Not relevant ☐	Less probably cover ☐	Not cover ☐
Equity	Important ☐	Probably important ☐	Not sure ☐	Probably not important ☐	Not important ☐	**If inequities could be reduced you would choose to:** Cover ☐	More probably cover ☐	Not relevant ☐	Less probably cover ☐	Not cover ☐
Cost-effectiveness	Important ☐	Probably important ☐	Not sure ☐	Probably not important ☐	Not important ☐	**If the cost per unit of benefit is low you would choose to:** Cover ☐	More probably cover ☐	Not relevant ☐	Less probably cover ☐	Not cover ☐
Budget	Important ☐	Probably important ☐	Not sure ☐	Probably not important ☐	Not important ☐	**If the impact on budget is low you would choose to:** Cover ☐	More probably cover ☐	Not relevant ☐	Less probably cover ☐	Not cover ☐

7) Are there other important factors that should be considered when making coverage decisions? If yes, please list them and explain how important they are and how they would impact on the coverage decision.

8) In your opinion, how important is it to have the following types of information available in a summary of findings of research about the effects of an intervention (that is intended to inform a coverage decisions by policymakers and managers)? (1=not important; 5=extremely important)

	Importance	Comments
Estimates of effects using quantitative results	1 2 3 4 5 ☐ ☐ ☐ ☐ ☐	
Confidence intervals for estimates of effects	1 2 3 4 5 ☐ ☐ ☐ ☐ ☐	
Descriptions of the size of effects in words (qualitative results)	1 2 3 4 5 ☐ ☐ ☐ ☐ ☐ 1 2 3 4 5 ☐ ☐ ☐ ☐ ☐	
How much evidence there is (the number of studies and/or participants) for each estimate of effect	1 2 3 4 5 ☐ ☐ ☐ ☐ ☐ 1 2 3 4 5 ☐ ☐ ☐ ☐ ☐	
The quality of the evidence for each estimate of effect (how confident we can be in)	1 2 3 4 5 ☐ ☐ ☐ ☐ ☐	

9) Considering the example attached, do you think the "Judgement" section is helpful to summarise the information presented and to take the decision?

10) Would you consider a system of grading the quality of evidence (from low to high) for the effects of an intervention (that is intended to inform a coverage decisions by policymakers and managers) desirable or undesirable? (By "quality of evidence" we mean a judgement about how confident we can be in estimates of those effects.) Are you aware of the availability of standardised systems to do that?

11) Do you think this framework could be a useful tool for policy makers and managers taking coverage decisions? Please explain

Appendix 2: Stakeholders' feedbacks

Feedback on DECIDE framework for going from evidence to coverage decisions

Purpose	The purpose of the framework is to help people responsible for coverage decisions to systematically and transparently consider factors that can (and should) influence decisions about whether to pay for the introduction of an intervention/option in a specific healthcare setting.
Coverage decision	Decisions by third party payers (public or private health insurers), which can take place at national and/or regional level, about whether and how much to pay for drugs, tests, devices or services and under what conditions.
Target audience	Policy makers, managers and their support staff with responsibility for making coverage decisions. Assuming that they have technical support to provide the evidence that is used in the framework.
Nature of evidence available to inform decisions	Typically complex information from diverse study designs regarding different aspects which could be relevant for the decision, with lots of uncertainty.
Decision making processes	Varies. Political or managerial processes. The use of research evidence is often optional and non-systematic.
Relevant factors	Factors that can determine the importance of paying for the introduction of an intervention/option and that should be considered as criteria in the framework for going from evidence to coverage decisions.
Evidence regarding costs	Cost-effectiveness and budget information are extremely relevant but often not available. Local costing studies are likely to be needed.

				Comments
Comprehensiveness				
1. Are there important relevant factors that are missing from the framework? If YES list them in the comments section.	Yes ☐	Uncertain ☐	No ☐	
Relevance				
2. Are there criteria included in the framework that should not have been? If YES list them in the comments section.	Yes ☐	Uncertain ☐	No ☐	
Applicability				
3. Is the framework applicable to different types of coverage decisions?	Yes ☐	Uncertain ☐	No ☐	
4. Is the framework applicable to different types of decision-making processes?	Yes ☐	Uncertain ☐	No ☐	
Simplicity				
5. Is the framework more complicated than necessary?	Yes ☐	Uncertain ☐	No ☐	
Logic				
6. Is the framework organised in a logical way that is easy to understand?	Yes ☐	Uncertain ☐	No ☐	
Clarity				
7. Are the criteria labelled and explained in a way that is easy to understand?	Yes ☐	Uncertain ☐	No ☐	
Usability				
8. Would it be easy for people responsible for coverage decisions to use the framework?	Yes ☐	Uncertain ☐	No ☐	
Suitability				
9. Is the framework suitable for informing and helping people to make coverage decisions?	Yes ☐	Uncertain ☐	No ☐	
Usefulness				
10. Is the framework likely to be useful to people responsible for coverage decisions?	Yes ☐	Uncertain ☐	No ☐	
Overall assessment				
11. Overall, is the framework adequate for its intended purpose?	Yes ☐	Uncertain ☐	No ☐	
Strengths				
12. What do you like about the framework?				
Weaknesses				
13. What don't you like about the framework and what suggestions do you have for improving it?				
Anything else				
14. Please include any other comments you have regarding the framework.				

Appendix 3: User testing

DECIDE WP2 User testing: EtD for policy makers and managers

Test person no.:	
Place:	
Date:	
Interviewer/notetaker:	

1. Checklist

For facilitator, bring:

- Printed copy / tablet version of EtD

For observer/note taker, bring:

- Paper and pen to take notes
- Tape recorder

2. Introduction and instructions

> *Go through the* written information they have already received

- What we are doing
- Who is participating, why we invited you
- How the test is conducted
- What happens to the data/recording
- Rights to quit or retract recording
- Questions?

> Turn on audiorecorder.

Background questions – 5 minutes

A	**Ask:** How many years of experience in decision making in healthcare setting do you have? .....Years of decision making experience
	Ask: What is your training in health research methodology (academic background)? ☐ Never done a formal course in HRM ☐ Done 1 or more formal courses but no masters/ Ph.D degree ☐ I have a masters/ Ph.D degree in HRM
	Ask: What is your background and current position? **Background:** ☐Medical ☐Psychological/Social ☐Legal ☐Administrative ☐Economic ☐Other (specify) **Current position:**

B	**Ask:** When you have to take a coverage decision and you don't know the answer to, what do you most often do? (Check all that apply if more than one action)
	☐ Consult a senior colleague or specialist ☐ Consult your staff ☐ Consult/organise specific commissions ☐ Consult guidelines or HTA documents ☐ Other, please specify:

C	**Ask:** How often do you on average consult guidelines when you're taking coverage decision?
	☐ Seldom or never ☐ Monthly ☐ Weekly

	☐ Daily

D	**Say:** Think to a coverage decision you were involved in. Explain **very briefly** what sort of information you needed to make an informed one.
	Notes:

Repeat instructions

No right or wrong answer
You are not being tested, it is our material we are testing.

There are no right or wrong answers to our questions.

If you think something is easy or difficult, clear or confusing, if you understand or don't understand, we just want to know about it.

Think out loud
Think out loud. Tell me what you are thinking, what you see, what you find confusing or surprising, even the least little bit. For instance:

- What you are looking at, describe your experience of it.
- If you are unsure about anything
- If you are surprised by anything
- If there are things you don't understand, just say "I don't know what this means…"

My role
My role is to ask questions. But, since it is your opinion we are interested in, I will be otherwise saying as little as possible.

If you have any questions not regarding navigational issues, I will try to answer them after the test.

Scenario

1	Let the participant select an appropriate clinical scenario with a question about therapy at the end. **Ask:** "Which of the following scenarios do you wish to look at?" (tick off for selected scenario) *Scenario 1 is about .....* ☐ *Scenario 2 is about .....* ☐ *Scenario 3 is about .....* ☐

The EtD table for policy makers and managers: first impressions

> Wait before showing the EtCD table, read first part of section 2:

2	**First impressions** **Say:** I'm going to show you what we call an Evidence to Coverage Decision table. We are most interested in the content and structure of the table you will be looking at. We would like your first immediate impression, your spontaneous reaction to it when I show it to you. Don't think, just tell me the first thing that comes into your head when you see it. ***> Now show the table.*** **Ask:** What is your first reaction? **Ask:** • Can you explain what it means to you, using your own words? • How easy is this table to understand?
Notes:	

The EtD table for policy makers and managers: detailed questions

3	**Table in more detail:** • Keep encouraging the participant to think aloud and to give his / her impressions. • We would like **you to comment of the individual components** (see below)	
Headers Decision header Column headings		Easy to understand? Helpful? Anything lacking? Anything superfluous?
Severity		Easy to understand? Helpful? Anything lacking? Anything superfluous?
Outcomes		Easy to understand? Helpful? Anything lacking? Anything superfluous?
Estimates		Explain in your own words what it means: Easy to understand? Helpful? Anything lacking? Anything superfluous?
Quality of evidence Certainty of the evidence		Explain in your own words what it means: Easy to understand? Helpful? Anything lacking? Anything superfluous?
Values and preferences		Explain in your own words what it means: Easy to understand? Helpful? Anything lacking?

	Anything superfluous?
Resource use	Easy to understand? Helpful? Anything lacking? Anything superfluous?
Equity	Easy to understand? Helpful? Anything lacking? Anything superfluous?
Feasibility	Easy to understand? Helpful? Anything lacking? Anything superfluous?
Balance of desireable and undesirable consequences	Easy to understand? Helpful? Anything lacking? Anything superfluous?
Decision	Easy to understand? Helpful? Anything lacking? Anything superfluous?
Notes:	

The EtD table for policy makers and managers: summing-up questions

4	***Summing-up questions***
	Summing up understandability ***Say:*** I would like to ask you a few questions about the information included in the table ***Ask:***What is the overall effect of the intervention? Can you elaborate where do you get your answer from? ***Ask:*** Did you find the information generally easy or difficult to understand?
	Summing up usefulness ***Say:*** The goal of this table is to provide additional information on those factors that are considered / pondered before taking a coverage decision, in a tabular format ***Ask:*** Is this table valuable or useful? ***Ask:*** Do you think this way of formating information would be useful for you and your collegues if you were going to take a coverage decision? (why?)
	Do you feel that the table is overall.... ☐ Totally useless ☐ Useless ☐ Somewhat Useless ☐ Undecided ☐ Somewhat Useful ☐ Useful ☐ Very usefull
	Summing up completeness ***Ask:*** After seeing this table, would you want to see more information for decision making? • What kind of information would you want to see? , in any particular circumstances?
	Do you feel that the table is overall.... ☐ Totally incomplete ☐ Incomplete ☐ Somewhat incomplete ☐ Undecided ☐ Somewhat complete ☐ Complete ☐ Very complete
	Summing up credibility ***Ask:*** If this table will be used in your institution to help taking coverage decisions, would you feel it is an add value or may gain credibility to users?

5	**Participants suggested alternative presentations of information** **Ask:** What do you think about the presentation of the information in this table? **Ask:** Do you think there could be a different ideal design of this table ? **Say:** Consider those things that particularly confused or frustrated you, you didn't like, you felt missing or especially liked you ***> Present the test subject with blank papers and ask them to draw their ideas or concepts.***

Say: Thank you very much – that's all. But we also would like your feedback on how we might have organised this session better. Any suggestions for improving the user testing?

Appendix 4: Systematic review of vaccines' frameworks

Additional file 1: Full-text articles excluded**.**

No decisional frameworks for community vaccine adoption:

- Abid N, Islam OU, Bosan A, Iqbal T, Darwish A, Bile KM: **Pakistan's fight against poliomyelitis: Introducing innovative strategies to address challenges and attain the goal of eradication.** *East Mediterr Health J* 2010, **16**(Suppl):S5-14.
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Additional file 2: Dimensions considered across conceptual frameworks and empirical approaches.

STUDIES	DIMENSIONS									
	Importance of illness or problem	**Vaccine characteristics (benefits and harms)**	**Values and preferences**	**Economic considerations/Resource use**	**Impact of vaccination**	**Acceptability**	**Feasibility**	**Equity and Ethical considerations**	**Legal and political considerations**	**Decision-making**
Ahmed et al., 2011 (17)		X	X	X						
Blecher et al., 2012 (18) Ngcobo and Cameron 2012 (21)	X	X		X			X			X
Brooks and Ba Nguz, 2012 (19) Milstien et al., 2010 (22)	X	X		X	X					X
Bryson et al., 2010 (26)	X	X		X		X	X			X
Burchett et al., 2012 (12)	X	X		X	X	X	X	X		X

STUDIES	DIMENSIONS									
	Importance of illness or problem	**Vaccine characteristics (benefits and harms)**	**Values and preferences**	**Economic considerations/Resource use**	**Impact of vaccination**	**Acceptability**	**Feasibility**	**Equity and Ethical considerations**	**Legal and political considerations**	**Decision-making**
Cho 2012 (25)	X	X		X			X			
Duclos et al., 2012 (20)	X	X		X			X	X	X	X
Levine et al., 2010 (23)	X	X		X	X		X	X	X	X
Makinen et al., 2012 (24)	X	X		X						X
Piatti2011 (27)	X	X		X				X	X	X
Piso and Wild 2009 (15)	X	X		X		X	X	X	X	X
Tapia-Conyer et al. 2013 (16)	X	X		X	X			X	X	X

STUDIES	DIMENSIONS									
	Importance of illness or problem	**Vaccine characteristics (benefits and harms)**	**Values and preferences**	**Economic considerations/Resource use**	**Impact of vaccination**	**Acceptability**	**Feasibility**	**Equity and Ethical considerations**	**Legal and political considerations**	**Decision-making**
Total	11	12	1	12	4	3	7	6	5	10

Additional file 3: Information considered across conceptual frameworks and empirical approaches.

DIMENSION	CRITERIA	STUDIES MENTIONING CRITERIA AND FREQUENCY												Tot
		Ahmed et al., 2011	Blecher et al., 2012 Ngcobo and Cameron 2012	Brooks and Ba-Nguz 2012 Milstien et al., 2010	Bryson et al. 2010	Burchett et al. 2012	Cho 2012	Duclos et al., 2012	Levine et al., 2010	Makinen et al., 2012	Piatti 2011	Piso and Wild 2009	Tapia-Conyer et al. 2013	
Importance of illness or problem	Burden of disease data				x	x			x	x		x	x	6
	Prevalence			x		x			x			x		4
	Incidence		x			x	x		x			x		5
	Mortality/Case fatality rates		x	x		x	x	x						5
	Morbidity		x			x		x						3
	Social Impact		x			x		x			x	x		5
	Hospitalizations					x								1
	Riskfactors										x	x		2
	Specificriskgroups			x		x		x			x	x		5
	Disease occurrence over time (i.e., epidemic, secular trends)							x						1
	Serogroups or serotypes distribution							x	x					2
	Clinical features of the disease						x	x				x		3
	Clinical management							x				x		2
	Cost of disease					x		x						2
	Perceptions of importance		x			x								2
	Other preventives											x		1

DIMENSION	CRITERIA	STUDIES MENTIONING CRITERIA AND FREQUENCY												Tot
		Ahmed et al., 2011	Blecher et al., 2012 Ngcobo and Cameron 2012	Brooks and Ba-Nguz 2012 Milstien et al., 2010	Bryson et al. 2010	Burchett et al. 2012	Cho 2012	Duclos et al., 2012	Levine et al., 2010	Makinen et al., 2012	Piatti 2011	Piso and Wild 2009	Tapia-Conyer et al. 2013	
	measures													
Vaccine characteristics (benefits and harms)	Vaccine characteristics									x		x		2
	Biological effects of the vaccine										x	x	x	3
	Vaccine efficacy and effectiveness	x	x	x	x	x	x	x	x		x	x	x	11
	Vaccine coverage										x			1
	Population impact of the vaccine							x						1
	Herd immunity							x						1
	Vaccine safety	x	x	x	x	x	x	x	x		x	x	x	11
	Interaction with other vaccines			x										1
	Indirect effects							x						1
	Cold chain and logistical concerns							x	x					2
	Vaccine administration schedule							x				x	x	3
	Social and programmatic acceptability of the schedule							x						1
Values and preferences	Relative importance of outcomes related to	x												1

DIMENSION	CRITERIA	STUDIES MENTIONING CRITERIA AND FREQUENCY												Tot
		Ahmed et al., 2011	Blecher et al., 2012 Ngcobo and Cameron 2012	Brooks and Ba-Nguz 2012 Milstien et al., 2010	Bryson et al. 2010	Burchett et al. 2012	Cho 2012	Duclos et al., 2012	Levine et al., 2010	Makinen et al., 2012	Piatti 2011	Piso and Wild 2009	Tapia-Conyer et al. 2013	
	benefits													
	Relative importance of outcomes related to harms	x												1
	Relative importance of outcomes related to cost	x												1
Economic considerations /Resource use	Health economic analyses (e.g., cost-benefit, cost-utility, cost-effectiveness)	x	x	x	x	x	x	x	x	x	x	x	x	12
	Direct and indirect cost										x			1
	Vaccine and vaccine delivery costs		x			x	x	x		x				5
	Potential for vaccine price reductions							x						1
	Affordability of immunization		x				x	x						3
	Cost-effectiveness of alternatives interventions			x		x					x			3
	Incremental costs					x								1
	Funding sources					x			x					2
	Financial sustainability					x	x		x					3
Impact of	Impact on health			x		x			x					3

DIMENSION	CRITERIA	STUDIES MENTIONING CRITERIA AND FREQUENCY												Tot
		Ahmed et al., 2011	Blecher et al., 2012 Ngcobo and Cameron 2012	Brooks and Ba-Nguz 2012 Milstien et al., 2010	Bryson et al. 2010	Burchett et al. 2012	Cho 2012	Duclos et al., 2012	Levine et al., 2010	Makinen et al., 2012	Piatti 2011	Piso and Wild 2009	Tapia-Conyer et al. 2013	
vaccination	outcomes													
	Impact on non-health outcomes					x			x					2
	Effect of co-administration					x								1
	Risk of serotype replacement					x								1
	Other impact					x								1
Acceptability	Acceptability of the vaccine					x						x		2
	Public perception				x									1
Feasibility	Feasibility of the implementation of the programme		x			x			x			x		4
	Feasibility of local vaccine production and vaccine availability				x			x	x					3
	Feasibility of recommendation				x				x					2
	Ability to reach the target populations							x	x					2
	Impact of vaccine adoption on the wider health system.							x				x		2

DIMENSION	CRITERIA	STUDIES MENTIONING CRITERIA AND FREQUENCY												Tot
		Ahmed et al., 2011	Blecher et al., 2012 Ngcobo and Cameron 2012	Brooks and Ba-Nguz 2012 Milstien et al., 2010	Bryson et al. 2010	Burchett et al. 2012	Cho 2012	Duclos et al., 2012	Levine et al., 2010	Makinen et al., 2012	Piatti 2011	Piso and Wild 2009	Tapia-Conyer et al. 2013	
	Ability to monitor programme impact (i.e., surveillance)						x	x	x			x		4
	Epidemiological changes of the disease (after vaccine introduction)											x		1
Equity and Ethical considerations	Ethical considerations							x			x	x		3
	Accessibility, equity and ethics					x			x		x			3
Legal and political considerations	Legal considerations							x	x		x	x	x	5
Decision-making	Decision-making process								x	x		x	x	4
	Evidence sources/ quality of evidences					x						x		2
	Impacts and coverage of other interventions for the disease			x				x				x		3
	Population coverage											x		1
	Priority										x			1
	Actors involved					x								1
	Procedures					x								1

DIMENSION	CRITERIA	STUDIES MENTIONING CRITERIA AND FREQUENCY												Tot
		Ahmed et al., 2011	Blecher et al., 2012 Ngcobo and Cameron 2012	Brooks and Ba-Nguz 2012 Milstien et al., 2010	Bryson et al. 2010	Burchett et al. 2012	Cho 2012	Duclos et al., 2012	Levine et al., 2010	Makinen et al., 2012	Piatti 2011	Piso and Wild 2009	Tapia-Conyer et al. 2013	
	Cues to action					x								1
	Recommendations of other countries				x									1
	International guidelines and expert advice		x											1
	Political process		x						x					2

Appendix 5: Evolution of the EtD framework over time

GRADE/DECIDE Evidence to Decision (EtD) framework – coverage decision

Should we stop covering prostate cancer opportunistic screening for asymptomatic men?

Patients: Asymptomatic men over 50 years
Intervention: Opportunistic screening with prostate specific antigen (PSA)
Comparison: No screening
Main outcomes: All-cause mortality, prostate cancer specific mortality, quality of life, harms, prostate cancer diagnosis (number of men diagnosed with prostate cancer)
Setting: The National Health Service in Italy
Perspective: Regional Health Authority

Background: **:** Prostate cancer is common and a leading cause of morbidity and mortality in men. It rarely leads to early, reliable warning signs or symptoms while still confined to the prostate gland. Effective early detection and treatment strategies in asymptomatic men could potentially provide a large benefit to many men. Screening aims to identify cancers at an early stage, thereby increasing the chances of successful treatment (resulting in improvements in survival and quality of life). However, many men will live with asymptomatic prostate cancer until they die from other causes. Detecting cancers that will never cause symptoms or death is referred to as overdiagnosis. Consequences of overdiagnosis include the negative effects of unnecessary labelling, the harms of unneeded tests and treatments, and the wasted opportunity costs. Over 30% of patients over the age of 50 currently receive opportunistic PSA testing in the Local Health Authority.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
PROBLEM	**Is the problem a priority?**	*Don't know* ☐ *Varies* ☐ *No* ☐ *Probably no* ☐ *Probably yes* ☒ *Yes* ☐ ***Detailed judgements***	Prostate cancer is the most commonly diagnosed cancer and the third leading cause of death in men in developed countries. Advanced age is the main risk factor: more than 75% of all prostate cancers are diagnosed in men aged 65 years and over. The vast majority of men with prostate cancer have no symptoms and their tumors are detected by routine testing. Lower urinary tract symptoms due to benign prostatic obstruction are common in elderly men and may result in increased concentrations of prostate specific antigen (PSA) but are not associated with an increased prostate cancer incidence. In most men prostate cancer is slowly growing and does not result in clinical signs or symptoms during their lifetime.	

BENEFITS & HARMS

How substantial are the desirable anticipated effects?

Don't know	**Varies**	Trivial	Small	Moderate	Large
☐	☐	☐	☒	☐	☐

Detailed judgements

How substantial are the undesirable anticipated effects?

Don't know	**Varies**	Large	Moderate	Small	Trivial
☐	☐	☒	☐	☐	☐

Detailed judgements

RESEARCH EVIDENCE

Summary of findings: *Screening vs no screening (Cochrane 2013)*

Outcome[1]	Control	Screening	Relative effect (RR) (95%CI)	Certainty of the evidence (GRADE)
All-cause mortality	21 per 100	21 per 100 (20 to 22)	**RR 1** (0.96 to 1.03)	⨁⨁⨁◯ Moderate[2]
Prostate cancer specific mortality	7 per 1000	7 per 1000 (6 to 8)	**RR 1** (0.86 to 1.17)	⨁⨁⨁◯ Moderate[3]
Prostate cancer diagnosis	68 per 1000	88 per 1000 (69 to 112)	**RR 1.3 (1.02 to 1.65)**	⨁⨁◯◯ Low[2,4]

[1] Information on costs, quality of life, metastatic disease at follow up, and harms of screening was limited and could not be meta-analyzed;
[2] Risk of bias was 'high' or 'unclear' for allocation concealment in 3 studies; 'high' or 'unclear' for random sequence generation in 2 studies; 'low' for blinding in all 4 studies; ' unclear' for incomplete outcome data in 2 studies; 'unclear' for selective reporting in 1 study;
and 'high' or 'unclear' for other bias in 2 studies.
[3] Risk of bias was 'high' or 'unclear' for allocation concealment in 4 studies; 'high' or 'unclear' for random sequence generation in 3 studies; 'unclear' for blinding of outcome assessment in 1 study; 'unclear' for incomplete outcome data in 2 studies; 'unclear' for selective reporting in 2 studies; and 'high' or 'unclear' for other bias in 3 studies.
[4] I2 = 98%; Chi2 = 162.78 (P <0.00001).

ADDITIONAL CONSIDERATIONS

Prostate cancer screening resulted in a range of harms that can be considered minor to major in severity and duration. Common minor harms included bleeding, bruising, and short-term anxiety. Common major harms included overdiagnosis and overtreatment, erectile dysfunction, and incontinence, infections, blood loss requiring transfusion, and pneumonia.
No evidence about quality of life available.

CERTAINTY

What is the overall certainty of the evidence of effects?

No included studies	Very low	Low	Moderate	High
☐	☐	☐	☒	☐

Detailed judgements

RESEARCH EVIDENCE

Moderate

ADDITIONAL CONSIDERATIONS

All-cause mortality and prostate cancer specific mortality are critical outcomes; prostate cancer diagnosis just an important one.

VALUES

Is there important uncertainty about how much people value the main outcomes?

No known undesirable outcomes	Important uncertainty	Possibly important uncertainty	Probably no important uncertainty	No important uncertainty
☐	☐	☐	☒	☐

Detailed judgements

RESEARCH EVIDENCE

A 2012 study (de Bekker-Grob 2012) aimed at determining men's preferences for prostate cancer screening found that men were willing to trade-off some risk reduction of prostate cancer related death to be relieved of the burden of biopsies or unnecessary treatments. Increasing knowledge on overdiagnosis and overtreatment, especially for men with lower educational level, is warranted to prevent unrealistic expectations from screening. The study results are based on a discrete choice experiment conducted among a representative sample of 1000 men (55-75 years old).

A 2008 study (Sanda 2008) aimed at identifying determinants of health-related quality of life after primary treatment of prostate cancer and measuring the effects of such determinants on satisfaction with the outcome of treatment. They prospectively collected outcomes

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
			reported by 1201 patients and 625 spouses or partners at multiple centers before and after radical prostatectomy, brachytherapy, or external-beam radiotherapy and evaluated factors associated with changes in quality of life within study groups and determined the effects on satisfaction with the treatment outcome. Each prostate cancer treatment was associated with a distinct pattern of change in quality of life domains related to urinary, sexual, bowel, and hormonal function. These changes influenced satisfaction with treatment outcomes among patients and their spouses or partners.	
BALANCE	**Does the balance between desirable and undesirable effects favour the intervention or the comparison?**	*No included studies* ☐ / ***Varies*** ☐ / *Favours the comparison* ☒ / *Probably favours the comparison* ☐ / *Does not favour either the option or the comparison* ☐ / *Probably favours the option* ☐ / *Favours the option* ☐ ***Detailed judgements***	See Summary of Findings	
RESOURCE USE	**How large are the resource requirements (costs)?**	*Don't know* ☐ / ***Varies*** ☐ / *Large costs* ☐ / *Moderate costs* ☒ / *Negligible costs or savings* ☐ / *Moderate savings* ☐ / *Large savings* ☐ **Detailed judgements**	See table below Data referred to year 2013 coming from Roma E Italian Local Health Authorities (population of 537,002 inhabitants). In this table both symptomatic and asymptomatic men are included.	
	What is the certainty of the evidence of resource requirements?	*No included studies* ☐ / *Very low* ☐ / *Low* ☐ / *Moderate* ☒ / *High* ☐ ***Detailed judgements***	The data about costs are derived from Local Health Authorities database, with the analysis of real patient information. The cost-effectveness analysis examined are consistent in evaluating the prostate cancer screening as a bad-value-for-money intervention.	

Age	Total population (age range)	N° of patients	N° of PSA performed	% patients	Single cost €	Total costs €
50-59	36781	6302	8754	17.1	7.41	64867.14
60-69	26975	9058	14631	33.6	7.41	108415.71
70-79	22461	11133	20275	49.6	7.41	150237.75
>79	13038	5929	10716	45.5	7.41	79405,56
	99255	**32422**	**54376**	**32.7**	7.41	**434781.16**

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
	Does the cost effectiveness of the intervention favour the intervention or the comparison?	*No included studies* ☐ / ***Varies*** ☐ / *Favours the comparison* ☒ / *Probably favours the comparison* ☐ / *Does not favour either the option or the comparison* ☐ / *Probably favours the option* ☐ / *Favours the option* ☐ **Detailed judgements**	Shteynshlyuger (2011) evaluated the cost-effectiveness of prostate specific antigen screening using data from the European Randomized Study of Screening for Prostate Cancer protocol extrapolated to the United States. They used Surveillance, Epidemiology and End Results-Medicare data and a nationwide sample of employer provided estimates of costs of care for patients with prostate cancer. This intervention would cost $262,758 per life-year saved (threshold study authors of $100,000/LYS). Shin S (2014) performed a cost-utility analysis on the adoption of PSA screening program among men aged 50-74-years in Korea from the healthcare system perspective. PSA screening is not cost-effective. Several data sources were used for the cost-utility analysis, including general health screening data, the Korea Central Cancer Registry, national insurance claims data, and cause of mortality from the National Statistical Office. Pataky R (2014) evaluated the cost-effectiveness of PSA screening, with and without adjustment for quality of life, for the British Columbia (BC) population. They adapted an existing natural history model using BC incidence, treatment, cost and mortality patterns. The model assumed mortality reduction consistent with the European Study of Randomized Screening for Prostate Cancer. All screening strategies resulted in a loss of quality-adjusted life years (QALYs).	.
EQUITY	**What would be the impact on health equity?**	*Don't know* ☐ / ***Varies*** ☐ / *Reduced* ☐ / *Probably reduced* ☐ / *Probably increased* ☒ / *Increased* ☐ **Detailed judgements**	No evidence found	We do not foresee negative impact on equity, actually the opposite.
ACCEPTABILITY	**Is the option acceptable to key stakeholders?**	*Don't know* ☐ / ***Varies*** ☐ / *No* ☐ / *Probably no* ☐ / *Probably yes* ☒ / *Yes* ☐ **Detailed judgements**	No evidence found	PSA in men over 50 is widely applied in Italy, so stopping covering this intervention could lead to problems of acceptability in: - men who already had screening; - men who ask for it because they used to know that it was a routine examination; - men with familial history of prostate cancer. Shared approach to decision-making between doctors and patients should be encouraged.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
FEASIBILITY	**Is the option feasible to implement?**	*Don't know* ☐ **Varies** ☐ *No* ☐ *Probably no* ☐ *Probably yes* ☒ *Yes* ☐ **Detailed judgements**	No evidence found	To stop covering an intervention that is routinely offered in everyday practice a shared approach to decision-making between doctors and patients should be put into place to clearly explain reasons for that. This process should be facilitated with the aid of appropriate patient education materials to promote informed patient choice and minimize workload among primary care providers and permitting primary care clinicians to focus on other preventive healthcare strategies of proven effectiveness for other health conditions.

Conclusions

	Do not cover	Coverage with evidence development	Coverage with price negotiation	Restricted coverage	Cover
Type of decision	☐	☐	☐	☒	☐

Decision Stop covering opportunistic screening for asymptomatic men, keep on covering just for the ones with familial history of prostate cancer.

Justification No evidence of efficacy on mortality in general male population >50 years. Minor and major adverse events such as bleeding, bruising, short term anxiety, overdiagnosis and overtreatment, erectile dysfunction and incontinence, infections, blood loss requiring transfusion, pneumonia.

Restrictions Coverage only for men with familial history of prostate cancer.

Implementation considerations

Monitoring and evaluation considerations

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Definitions for ratings of the certainty of the evidence (GRADE)**

Ratings	Definitions
⨁⨁⨁⨁ High	This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different* is low.
⨁⨁⨁◯ Moderate	This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different[4] is moderate.
⨁⨁◯◯ Low	This research provides some indication of the likely effect. However, the likelihood that it will be substantially different[4] is high.
⨁◯◯◯ Very low	This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different[4] is very high.

*Substantially different: large enough difference that it might have an effect on a decision

**The Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group began in the year 2000 as an informal collaboration of people with an interest in addressing the shortcomings of present grading systems in health care. The working group has developed a common, sensible and transparent approach to grading quality of evidence and strength of recommendations. Many international organizations have provided input into the development of the approach and have started using it.

(Return)

GRADE DECIDE

Prepared by: **WP2**
Date: **April 2013**

Should New Oral Anticoagulants (NOACs) be covered for patients with atrial fibrillation?

Patients: Patients with atrial fibrillation
Intervention: NOACs
Comparison: Warfarin

Background: Atrial fibrillation (AF) is the most common form of cardiac arrhythmia . 85 to 90% of cases occur as non-valvular AF , whereas only a small proportion of patients is associated with rheumatic valve disease (predominantly mitral stenosis) . In Italy, the AF has a prevalence of 1 to 2 % (which increases with age , reaching around 8% in subjects over 80 years), and an incidence of approximately 3 cases per 1000 person years / person , while the average age of patients with AF is about 77 years. Approximately 70 % of patients with AF have an age between 65 and 85 years . AF increases the risk of ischemic stroke by about 5 times , and stroke associated with AF have increased morbidity and mortality compared to those with different etiology .

Warfarin: The standard of care for the prevention of ischemic stroke in patients with AF is warfarin which may reduce the risk by 64% . Warfarin however increases the risk of major and intracranial bleeding that, depending on the studies of drugs and analyzed , respectively, varies from 1 .3 % to 3.6 % per year , and from 0.2 % to 0.5% per year . The use of warfarin requires a periodic control of the International Normalized Ratio (INR), and has a number of interactions with other drugs and certain foods that can enhance or reduce the anticoagulant action . If there is a need to quickly neutralize the action of warfarin (bleeding), vitamin K can be used as an antidote.

New oral anticoagulants (NOACs): This includes 2 classes of drugs : inhibitors of factor Xa (FXa) and direct thrombin inhibitors (DTIS) . Being endowed with a more predictable anticoagulant effect compared to warfarin, they have the advantage of not requiring periodic checks of blood coagulation , while requiring a routine monitoring of possible adverse effects . The main cause of concern during the use of NOACs is the absence of antidotes able to rapidly neutralize the action in case of need . This problem can be particularly serious in the presence of a reduced clearance of the drug, as in the elderly or in patients with impaired renal function . The FXa include rivaroxaban , apixaban , dabigatran , edoxaban , and betrixaban . All studies related to NOACs included patients with non-valvular AF , ie, in which a possible valvulopathy was not clinically significant . In Italy, for today dabigatran is already on prescription , and the rivaroxiban it will be soon, as it has passed the scrutiny of the Committee Pricing and Reimbursement AIFA .

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
BURDEN OF ILLNESS OR PROBLEM	**Is the condition severe?**	*No* ☐ / *Uncertain* ☐ / *Yes* ☐	The risk of complications varies depending on how well INR is controlled with Warfarin. Average risks are 8.1% for death, 2.5% for nonfatal stroke, and 7% for nonfatal major extracranial bleeds over two years in the RE-LY (Randomised Evaluation of Long-Term Anticoagulation Therapy) trial.	

GRADE DECIDE

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
BENEFITS, & HARMS	**Are the desirable anticipated effects large?**			**The study included** 3 randomized, controlled trials (RCTs) comparing NOACs with warfarin for management of AF and observational studies and FDA reports on adverse effects.
	Are the undesirable anticipated effects small?			**RCT patients characteristics** 50,578 patients; mean age >70ys; 63% men; CHADs2 index average 2,1 in the studies evaluating dabigatran and apixaban and 3,5 in the rivaroxaban studies. In the warfarin group the percentage of time in the INR target range was 55% to 66%.

Favour to Warfarin	*Uncertain*	*Favour to NOACs*
☐	☐	☐

Favour to Warfarin	*Uncertain*	*Favour to NOACs*
☐	☐	☐

	Effect Estimate		*Effect Judgement*					
Critical Outcomes	*Relative Risks*	*Absolute Risks*	*Large or Modest benefit*	*Small benefit*	*No effect*	*Small harm/ burden*	*Modest or Large harm/ burden*	*Quality of Evidence*
BENEFIT								
1. All-cause mortality	RR 0.88 (0.82-0.96)	8 fewer death/1,000 patients (3 to 11 fewer)	☐	☐	☐	☐	☐	HIGH ⊕⊕⊕⊕
2. VTE related	RR 0.77	NS	☐	☐	☐	☐	☐	MODERATE

GRADE DECIDE

What Is the overall certainty of this evidence (for our setting)?

Very Low	Low	Moderate	High
☐	☐	☐	☐

mortality	(0.57-1.02)							⊕⊕⊕⊖
3. Ischemic stroke	RR 0.89 (0.78-1.02)	NS	☐	☐	☐	☐	☐	MODERATE ⊕⊕⊕⊖
4. Hemorrhagic stroke	RR 0.48 (0,36-0.62)	4 fewer hemmorrhagic stroke/ 1,000 pts (2 to 5 fewer)	☐	☐	☐	☐	☐	MODERATE ⊕⊕⊕⊖
ADVERSE EFFECT								
1.Fatal bleeding	RR 0.60 (0.46-0.77)	1 fewer death/1,000 patients	☐	☐	☐	☐	☐	MODERATE ⊕⊕⊕⊖
2. Major bleeding	RR 0.80 (0.63-1.01)	NS	☐	☐	☐	☐	☐	LOW ⊕⊕⊖⊖
3.Gastrointesinal bleeding	RR 1.30 (0.97-1.73)	NS	☐	☐	☐	☐	☐	LOW ⊕⊕⊖⊖
4. Myocardial infarction	RR 0.95 (0.81-1.11)	NS	☐	☐	☐	☐	☐	LOW ⊕⊕⊖⊖
5.Discontinuation due to adverse effects	RR 1.23 (1.05-1.44)		☐	☐	☐	☐	☐	LOW ⊕⊕⊖⊖
6. Liver disfunction	RR 0.82 (0.56-1.18)	NS	☐	☐	☐	☐	☐	LOW ⊕⊕⊖⊖

Subgroup analysis reported in 1 study no differential effects on stroke prevention (interaction effects) for individuals with a history of cerebrovascular accidents, impaired renal function, or older age. However, these analyses suggest that, compared with warfarin, dabigatran may increase some bleeding complications in patients older than 75 years and in those receiving warfarin who have good control. The effects of impaired renal function were mixed, showing no interaction effect in one analysis and a differential risk for gastrointestinal bleeding with rivaroxaban in another.

In 2011, the FDA issued a notice that it was evaluating reports of **serious bleeding** with dabigatran.

For **myocardial infarction** in a subgroup analysis, the risk was increased with dabigatran (RR, 1.35 [CI, 0.99 to 1.85]) compared with FXa inhibitors (RR, 0.84 [CI, 0.70 to 1.01]) (*P* _ 0.010).

In subgroup analysis, rates of **discontinuation** were higher for dabigatran than for FXa inhibitors.

Burden of treatment
Warfarin: daily medication, lifestyle limitation, dietary restrictions,frequent blood testing and clinical visit
NOACS: Apixaban: twice daily medication, Dabigatran: twice daily medication, Rivaroxaban: daily medication.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
VALUES	**How certain is the relative importance of the desirable and undesirable outcomes?**	*A little* ☐ *Uncertain* ☐ *Highly* ☐	***Quality of life measurement*** *(measured with* Long-term utilities using *EuroQol ranging from death=0 to perfect life =1)* Atrial fibrillation 0.81 Sullivan (2006)93 Previous minor stroke 0.75 Gage (1996)94 Previous intracerebral hemorrhage 0.75 Gage (1996)94 Previous major stroke 0.33 Gage (1996)94 **Perspectives of patients on anticoagulation therapy** Patients at high risk for atrial fibrillation placed more value on the avoidance of stroke and less value on the avoidance of bleeding than	**Quality of life information** The impact of stroke outcome persists over a longer period of time (in term of disability) while other events are associated with impacts to quality of life that effect a finite period of time. It is assumed that there are minimal long term implications associated with bleeding events.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
	Would patients/caregivers feel that the benefits outweigh the harms and burden?	*No* ☐ *Uncertain* ☐ *Yes* ☐	did physicians who treat patients with atrial fibrillation. The views of the individual patient should be considered when decisions are being made about antithrombotic treatment for people with atrial fibrillation.	**Perspectives of patients on anticoagulation therapy** A prospective observational study measured physicians' and patients' thresholds for how much reduction in risk of stroke is necessary and how much risk of excess bleeding is acceptable with antithrombotic treatment in people with atrial fibrillation i**n t**ertiary and peripheral referral centres in Nova Scotia, Canada on 63 physicians who were treating patients with atrial fibrillation and 61 patients at high risk for atrial fibrillation. Thresholds were determined for the minimum reduction in risk of stroke necessary and the maximum increase in risk of excess bleeding acceptable for treatment with aspirin and warfarin in people with atrial fibrillation.

GRADE DECIDE

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
RESOURCE USE	**Is the incremental cost small relative to the net benefits?**	No ☐ Uncertain ☐ Yes ☐	See table below	Objective of the cost-effectiveness analysis is to compare the cost differences compared to the differences in effectiveness. A value below € 40,000 per year of life can be considered a "good investment" of healthcare resources. In this case, if we consider a life expectancy of 5 years (very conservative figure), the final value is around € 10,000 per life-year saved. So NOACs can be considered as a value for money.. These results are confirmed by the recent study published in 2013 (Harrington, 2013) n where the NAO have proved cost effective.
	Is the total cost (impact on budget) small?	No ☐ Uncertain ☐ Yes ☐	**Total drug cost for 100,000 patients**	

	Yearly costs per patient		
	Warfarin	*NOACs*	*Difference*
Drugs (0,1€/die for warfarin 2€/die for NOACs)	36,5€	730€	
INR test (including blood collection - 6€ twice month)*	144€	-	
Drugs and monitoring costs	180,5€	730€	549,5€
Hospitalization (13 admission/1,000 pts fewer for NOACs – considering 20,000 € per admission and 2 years of follow RCTs)		-260€ total and -130€ per year	-130€
Total costs			**419,5€ more for NOACs per patient**
Cost effectiveness			**419,5€ to save 9 patients every 1,000 treated** **46,61€ per life saved*** **

*We considered no difference in visits

**Hospitalization included outcome that present statistically significant difference (All cause mortality, fatal bleeding and ischemic stroke).

	Yearly costs per 100,000 patient		
	Warfarin	*NOACs*	*Difference*
Drugs and monitoring costs	14,400,000€	73,000,000€	58,600,000€
Total costs (including hospitalization)	- -	-13,000,000€	45,600,000€ more for NOACs

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
EQUITY	**What would be the impact on health inequities?**	*Increase* ☐ | *Uncertain* ☐ | *Reduction* ☐		To evaluate the impact on inequalities, the patient's pathway should be considered: Warfarin / NAO Diagnosis: X / X Visits: X / X Drug: X / X INR measurment: X / - Hospitalisations: X / X NOACs can have a positive impact on the patient pathway due to the elimination of the INR measurement, especially for all the people who have trouble constantly monitoring this value. The problem of the lack of an antidote for the NAO can lead to an increase of inequalities for those who, suffering an adverse event during their administration, are not able to cope with the rehabilitation process.
FEASIBILITY	**Is the option feasible to adoption in the actual setting?**	*No* ☐ | *Probably no* ☐ | *Uncertain* ☐ | *Probably yes* ☐ | *Yes* ☐		It might be difficult to restrict the use of NOACs to people who would benefit sufficiently to warrant the cost. Compliance potentially might be more of a problem with Dabigatran than Warfarin since monitoring and frequent clinic visit are not needed, but there's no evidence to support or refuse this. There is currently no antidote for NOACs. This is a concern for healthcare providers who have to manage bleeding patients receiving these drugs and may led to worse outcome in such patients.

GRADE DECIDE

Balance of desireable and undesirable consequences of covering the intervention	Undesirable consequences *clearly outweigh* desirable consequences	Undesirable consequences *probably outweigh* desirable consequences	The balance between desirable and undesirable consequences is *closely balanced* or *uncertain*	Desirable consequences *probably outweigh* undesirable consequences	Desirable consequences *clearly outweigh* undesirable consequences
	☐	☐	☐	☐	☐

Decision	**Do not cover**	**Coverage with evidence development (which Drug/s?)**	**Cover (which Drug/s?)**
	☐	☐	☐

Comments

Restriction
(any restriction on coverage of the intervention)

Justification
(reason for deciding the intervention should be covered, covered with evidence development or not covered)

Implementation considerations
(details regarding the decision, including any restrictions on coverage and conditions for coverage with evidence development)

References

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GRADE DECIDE

Prepared by WP: September 2013

Should MRI be dis-covered for patients aged >50 with undiagnosed knee problems?

Patients: Patients >50 with undiagnosed knee problem

Intervention: MRI

Comparison: Clinical examination

Background: In Italy magnetic resonance imaging (MRI) for undiagnosed knee problems can be prescribed directly by GPs without restriction of age or necessity of orthopedic consultation.

Despite evidence for the technical and diagnostic performance of MRI for patients with injuries to the menisci and cruciate ligaments, there is uncertainty about whether and when it should enter the diagnostic pathway for patients with suspected internal derangement of the knee. In the asymptomatic population 30% of people present meniscal tear if scanned with MRI and this number grows with age, this means there's room for over-diagnosis and inappropriate use of MRI especially in people aged >50 with undiagnosed knee problems.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
BURDEN OF ILLNESS OR PROBLEM	**Is the condition severe?**	*No* ☐ *Uncertain* ☐ *Yes* ☐	About one quarter of people over the age of 55 will report a significant episode of knee pain in the past year. Approximately half of these report has some associated disability. Painful knee osteoarthritis associated with mild to moderate disability affects up to 10% of adults aged over 55.(1) Treatment of OA generally involves a combination of exercise, lifestyle modification, and analgesics and anti-inflammatory drugs. The role of arthroscopy is debated. If pain becomes debilitating, joint replacement surgery may be used to improve the quality of life. In this group of people is also common to have asymptomatic knee derangement, for example (2):	

	Proportion with asymptomatic meniscal tear or destruction	
Age group	Men	Women
50-59 years	32%	19%
60-69 years	46%	40%
70-90 years	56%	51%

GRADE DECIDE

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
BENEFITS & HARMS	**Are the desirable anticipated effects large?**	No ☐ Uncertain ☐ Yes ☐		The data presented come from a randomized trial (DAMASK) in which a total of 553 patients, seen by UK GPs for undiagnosed knee pain, were enrolled over a period of about 2 years. The purpose of the study was to evaluate the effectiveness of GP referral to early MRI and a provisional orthopaedic appointment, compared with referral to an orthopaedic specialist without prior MRI for patients with continuing knee problems. A secondary outcome of the DAMASK trial was to assess the effect of early access to MRI, compared with referral to an orthopaedic specialist, on GPs' diagnoses and treatment plans for patients with knee problems. The results show that the MRI does not significantly change the diagnoses and treatment plans, but it increases the confidence of the GP's own decisions and actions. Burden of treatment: the MRI findings that mainly affects the clinical strategy is meniscal tear, infact patient diagnosed with a meniscal tear is very likely to undergo arthroscopic surgery. Due to the high rate of asymptomatic meniscal tear there is risk for useless/inappropriate treatment. A study of 991 subjects (Englund 2008) assessed the prevalence of meniscus injuries in the population over 50 and found that 23% of people without knee pain and osteoarthritis showed no evidence of meniscus injuries encountered with resonance and that this percentage rose to 60 % in people with osteoarthritis always asymptomatic.
	Are the undesirable anticipated effects small?	No ☐ Uncertain ☐ Yes ☐		
	What is the overall certainty of this evidence (for our setting)?	High ☐ Moderate ☐ Low ☐ Very Low ☐		

	Effect size		
Outcomes	***Mean difference***	***Statistical significance***	***Quality of Evidence***
1. SF-36 Physical functioning	2.81* (-0.26 to 5.89)	Non statistically significant	LOW[1] ⨁⨁⨀⨀
2. KQoL-26 Physical functioning	3.65* (1.03 to 6.28)	P-value=0.007	LOW[1] ⨁⨁⨀⨀
3. Days off work	No days off work in both groups.		LOW[1] ⨁⨁⨀⨀

[1]Quality of evidence was downgraded for indirectness because the study population is different from the PICO's one: only UK participants, mean age years 39/40 (SD=10).

*** For both outcomes the threshold of difference between the two scores considered clinically relevant (6.75) has not been reached.**

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
VALUE	**Would patients/caregivers feel that the benefits outweigh the harms and burden?**	*No* ☐ *Uncertain* ☐ *Yes* ☐	A cross-sectional survey of 2001 investigated the magnitude of effect of the patient's perceived need for radiological examinations (plain film, computed tomography and MRI) on use of those services. Results show a significant association between patient's perceived need of those examinations and service usage and this may partially reflect differences in physicians' adherence to guidelines. This suggests that effort to educate patients about when radiological studies are indicated may be an important complement to practice guideline. (6) A study of 2008, using a qualitative descriptive design, collected data from 27 patients undergoing total knee replacement (17 pre-operative focus groups and 10 post-operative single interviews). Results showed that participants delayed surgery for months to years despite increasing pain and limitation and once decided for surgery, participants entered a period of waiting and worrying about what would happened before and after surgery. (7)	These two studies on values and preferences of patients about radiological examinations and knee surgery include population and clinical problems that differ from the ones of our clinical question, so their results should be considered carefully when making judgments for our topic.

	CRITERIA	JUDGEMENTS	RESEARCH EVIDENCE	ADDITIONAL INFORMATION
RESOURCE USE	**Is the incremental cost small relative to the net benefits?**	*No* ☐ *Uncertain* ☐ *Yes* ☐		Cost-effectiveness issues related to the dis-coverage of MRI for people aged >50 with undiagnosed knee problem involve 1. effectiveness/appropriateness; 2. costs and 3. possible side effects: 1. performing an MRI in people aged >50 could be inappropriate and potentially not effective in detecting the right therapeutic strategy to solve the problem (see Benefit&Harms); 2. MRI is an expensive technique (see budget below); 3. side effect of dis-covering MRI in these patients could be a delay in the diagnosis of meniscal tears or rare tumours of the knee and osteonecrosis. Dis-coverage compared to coverage of MRI in people aged >50 with undiagnosed knee problem seems to be a dominant (more effectivess and less cost than alternative) and cost effective compared to coverage.

	Is the total cost (impact on budget) small?	*No* ☐ *Uncertain* ☐ *Yes* ☐	Calculation was based on data of Roma E Italian Local Health Authorithies with a population of 537,002 inhabitants. We consider: the dis-coverage of MRI (less cost), - 2,258,885 euros the surgical procedure saved following inappropriate MRI (less cost) - 2,457,045 euros specialist visit if patient does not make MRI (more cost) +1,047,165 euros 30% of patient with specialist visit have 1 MRI (3,765 patients) + 568,492 euros 30% of the 12,549 patients have 1 arthroscopy (1,129 patients) +1,920,074 euros --- **TOTAL SAVINGS EVERY 537,002 PATIENTS - 1,180,199 euros** **Dis-coverage MRI** We consider the procedure prescribed to >50 years patients by GPs: (14959 patients * 151 euros per each MRI) = - 2,258,885 euros **Surgical procedure saved** We consider that 30% of asymptomatic meniscal tear or destruction diagnosed with MRI undergo surgical intervention (50-64 years 25%; 65-74 years 63%); patients >75 were excluded: (1,445 patients * 1,700 euros)= - 2,457,045 euros **Specialist visit** We consider that if patients are not prescribed with a MRI, they will probably be referred to specialist visits: (14,959 patients * 70 euros) = + 1,047,165 euros We considered also that, after the specialist visit, 30% of these patients (excluding the ones >75) will undergo a MRI and 30% of this a consequent arthroscopic surgery.	
EQUITY	**What would be the impact on health inequities?**	*No* ☐ *Uncertain* ☐ *Yes* ☐		Equity issues related to the massive prescription of MRI involve 1. waiting lists problems and 2. over-diagnosis: 1. potential reduction of MRI prescription deriving from restriction to coverage for people aged >50 should lead to a positive decrease of waiting lists; 2. due to the high prevalence of asymptomatic knee damages in this population, the use of MRI could lead to over-diagnosis and consequent over-treatment (surgery): limiting the MRI prescription should reduce the risk of over-diagnosis.

FEASIBILITY	**Is the option feasible to adoption in the actual setting?**	*No* ☐ *Uncertain* ☐ *Yes* ☐		Feasibility issues related to the dis-coverage of MRI for people aged >50 involve 1. expertise needed for clinical assessment, 2. impact on the waiting list for specialist visits, 3. necessity of a standardised clinical pathway for the patient >50 with undiagnosed knee problems : 1. there could be a problem of expertise/ability to perform a proper clinical examination to diagnose knee problems especially among GPs. Training should be offered to guarantee the best performance for the patients; 2. limiting the possibility to prescribe MRI in people aged >50 could lead to an increase in prescription of specialist visit for these subjects, strategies should be put in action to avoid this; 3. the restriction to the prescription of MRI in this specific population should be supported by a standardised clinical pathway that both GPs and specialist should follow and share with patients, to guarantee the best approach to the problem.

Balance of desireable and undesirable consequences of dis-covering the intervention	Undesirable consequences *clearly outweigh* desirable consequences	Undesirable consequences *probably outweigh* desirable consequences	The balance between desirable and undesirable consequences is *closely balanced* or *uncertain*	Desirable consequences *probably outweigh* undesirable consequences	Desirable consequences *clearly outweigh* undesirable consequences
	☐	☐	☐	☐	☐

Decision	**Cover**	**Coverage with evidence development**	**Dis-Cover**
	☐	☐	☐
Comments			

Restriction
(any restriction on coverage of the intervention)

Justification
(reason for deciding the intervention should be covered, covered with evidence development or not covered)

Implementation considerations
(details regarding the decision, including any restrictions on coverage and conditions for coverage with evidence development)

References

1) Peat G, McCarney R, Croft P: Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann Rheum Dis 2001; 60:91–97.
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GRADE DECIDE

GRADE DECIDE Evidence to coverage decision framework

Prepared by: WP2 November 2012

Patients: high-risk infants and young children

Intervention: palivizumab

Question Should Palivizumab be covered for immunoprophylaxis of respiratory syncytial virus (RSV) bronchiolitis in high-risk infants and young children?

Background. RSV causes outbreaks of respiratory tract infection in temperate areas, especially in the winter months. It can affect people of any age and is usually a mild, self-limiting illness. It is most serious in infants and young children, in whom it is the single most important cause of lower respiratory tract infection (LRTI). RSV infection can present with a wide range of severity from mild respiratory symptoms, to rhinitis and otitis media, through to bronchiolitis, trachea-bronchiolitis and pneumonia. The diagnosis of bronchiolitis is based only on clinical signs and symptoms.

Approximately 4%-11% of infants and young children develop bronchiolitis during the first three years of life. Among those approximately 50% are infected by RSV (data from Italy).

The virus is spread by contaminated nasal secretions via respiratory droplets, so close contact with an infected individual or contaminated surface is required for transmission. RSV can persist for several hours on toys or other objects. Risk factors for RSV infection include crowding, low socioeconomic status, exposure to tobacco smoke and admission to hospital during the RSV season (late autumn to early spring). The children most at risk from severe disease if infected with RSV are infants under 6 weeks old or who have chronic lung disease (CLD), congenital heart disease (CHD) or immunodeficiency, and those born prematurely (at 35 weeks gestational age or before).

The therapy for bronchiolitis due to RSV infection, both of moderate and severe degree, is based on ventilatory support and adequate hydration. The efficacy of ribavirin is uncertain. The prognosis is almost favorable.

Passive Prophylaxis with high-tittered human polyclonal RSV IVIg does not significantly reduce the incidence of RSV infections. However, monthly prophylaxis significantly reduced the severity of RSV infections in very young high-risk patients, reduce the hospitalization rates and significantly shorter hospital stays compared to well-matched control patients.

No vaccines are available.

Palivizumab is the only licensed product available for prevention of RSV lower respiratory tract disease in infants and children with CLD, with a history of preterm birth (<35 weeks' gestation), or with haemo-dynamically significant CHD. Palivizumab is a humanized murine monoclonal anti-F glycoprotein immunoglobulin with neutralizing and fusion inhibitory activity against RSV and it is administered intramuscularly at a dose of 15 mg/kg once every 30 days.

	Criteria	Judgement	Research evidence	Additional Information
Burden of illness or Problem	**Is it severe?**	*No* ■ *Uncertain* ☐ *Yes* ☐	Most of the infected children develop respiratory distress of low or moderate degree. In Italy the hospitalization for bronchiolitis ranges from 0,6% to 5% of infants and young children during the first three years of life. Among those children about 30%-50% are infected with RSV (children both from high and low risk) This variability is attributable to the different criteria for hospitalization and different tests used to diagnose the RSV infection. The duration of hospitalization ranges from 5 to 6 days in Italy. Mortality due to bronchiolitis is less than 1% in children infected with RSV without underlying illness (USA). Mortality due to LRTI in those infected with RSV with heart and lung disease who are hospitalised is estimated to be around 3–5%.5 (USA). On those bases about 6 deaths due to RSV infection are expected in the cohort of Italian newborns per year.	

GRADE DECIDE

Benefits & harms

Overall, are the desirable effects large?

No	*Uncertain*	*Yes*
☐	■	☐

It is uncertain whether palivizumab reduce incidence of RSV hospitalization, days hospitalized, need of oxygen therapy, ICU hospitalization rate, need in mechanical ventilation and mortality when measured in the population as whole both in premature children with or without CLD children, in children with CHD and in children with cystic fibrosis. It is also uncertain whether palivizumab reduce the incidence of the outcome above mentioned in subgroup of population analysed.

A=overall population
B=children of gestational age ≤ 24months old haemo-dynamically significant CHD and unoperated or partially corrected CHD
C=children without CLD
D=children with CLD
E=children of gestational age 32-35 weeks
F=children of gestational age <32 weeks
G=non-cyanotic children
H=cyanotic children

Outcome	Results	GRADE
Reduction in mortality	A, B: Inconclusive compared to placebo	⊕⊖⊖⊖ VERY LOW
Reduction in incidence of bronchiolitis	A, B: Not measured	NOT EVALUABLE
Reduction in long term complications	A, B: Not measured	NOT EVALUABLE
Reduction in ICU hospitalization rate	A, B: Inconclusive compared to placebo	⊕⊕⊕⊖ MODERATE
Reduction in need of mechanical ventilation	A, B: Inconclusive compared to placebo	⊕⊕⊕⊖ MODERATE
Reduction in days hospitalized for bronchiolitis	A: 42% reduction in risk compared with placebo (the difference in duration of hospitalization <1 day) B: 56% reduction in risk compared with placebo (the difference in duration of hospitalization <1 day)	⊕⊕⊕⊖ MODERATE
Reduction in incidence of RSV hospitalization	A: 55% reduction in risk compared with placebo B: 45% reduction in risk compared with placebo C: 78% reduction in risk compared with placebo D: 39% reduction in risk compared with placebo E: 80% reduction in risk compared compared with placebo F: 47% reduction in risk compared with placebo G: 58% reduction in risk compared with placebo	⊕⊕⊖⊖ LOW

GRADE DECIDE

	Overall, are the undesirable effects small?	*No* ☐ *Uncertain* ■ *Yes* ☐	<table><tr><th>Outcome</th><th>Results</th><th>GRADE</th></tr><tr><td>Any adverse event</td><td>Inconclusive compared to placebo</td><td>⊕⊕⊖⊖ LOW</td></tr></table> These data come from a HTA document published in 2011 and a SR published in 2010.The documents include RCTs affected by several methodological flaws that leid their quality of evidence to be judge, using GRADE criteria, as LOW. That's why it is uncertain if the undesirable effects are small. These data are related to all of the populations considered in evaluating the estimate of beneficial effects	
Quality of evidence	**Overall, what is the certainty of the anticipated effects (in our setting)?**	*Very low* ■ *Low* ☐ *Moderate* ☐ *High* ☐	It is uncertain whether palivizumab reduce incidence of RSV hospitalization, days hospitalized, need of oxygen therapy, ICU hospitalization rate, need in mechanical ventilation and mortality when measured in the population as whole, both in premature children with or without CLD children, in children with CHD and in children with cystic fibrosis. It is also uncertain whether palivizumab reduce the incidence of the outcome above mentioned in subgroup of population analysed. The information for this judgment come from form the HTA (reporting the data coming from the IMpact-Study RSV Group 1998 and Feltes,2003) and the SR mentioned above. The overall quality of evidence in this case turns out to be VERY LOW, following GRADE criteria	
Value	**Would patients/caregiver feel that the benefits outweigh the harms?**	*Majority would not* ☐ *Uncertain* ■ *Majority would* ☐	Values of caregiver (i.e.anxiety) could play an important role , especially where are present variation in local health care organization and/or geographical barriers	
Resources	**Is the cost small relative to the net benefits?**	*No* ■ *Uncertain* ☐ *Yes* ☐	A recent HTA (Wang 2011) calculated the cost effectiveness for different subgroups, but the authors recognized that there is a poor quality estimates. This data showed that prophylaxis with palivizumab does not represent good value for money based on the current UK incremental cost-effectiveness ratio threshold of £30,000/QALY when used unselectively in children without CLD/CHD or children with CLD or CHD. In summary, the cost effective subgroups (< £30,000/QALY) for children who had no CLD or CHD must contain at least two other risk factors apart from Gestational age and birth age. The cost-effective subgroups for children who had CLD or CHD do not necessarily need to have any other risk factors.	
	Is the total cost (impact on budget) low?	*No* ■ *Uncertain* ☐ *Yes* ☐	For a mean patient of 5 kg, the costs of palivizumab is 3.376 € per patient per year. (15mg/kg x patient of 5 kg x 5 doses per season x 8,95 €/g – hospital price). Including the cost of palivizumab, the cost of drug administration and the savings in hospital stay, it was estimated an incremental cost per patient per season of nearly 4.200 € (Wang)	

Equity	**What would be the impact on health inequities?**	*Increased* ☐ *Probably increased* ■ *Little or uncertain* ☐ *Probably reduced* ☐ *Reduced* ☐	The intervention might only be available to those able to pay if it is not covered by insurance/NHS.	
Feasibility	**Is the option feasible to adoption in the actual setting?**	*No* ☐ *Probably no* ☐ *Uncertain* ☐ *Probably yes* ☐ *Yes* ☐	Possible difficulties in professional acceptability due to the large variability in prescribing palivizumab on the basis of the risk factors that can make the children eligible for the prophylaxis, the uncertainties related to the initiation and termination of immunoprophylaxis and the correct definition of the risks of the prognostic factors for hospital admission due to RSV infection (barriers due to Scientific Professional Association and its recommendation in different guideline; barriers due to Association of Patients and/or Caregivers; defensive medicine; legal constraint) Possible organisational impact in case of hospital –based instead of home –based palivizumab administration to all of the possible children eligible for prophylaxis (local health care organization and mission). Regulation constraint (by EMA or AIFA in Italy).	More than 20 risk factors have been noted in the literature as increasing either the risk of acquiring an RSV infection or the risk of more severe RSV disease in infants and young children. A review of the literature demonstrates that most of these factors are not found consistently from one study to another and many have only a small impact on risk. All of the included studies were observational and many of those of very low quality. The risk factors that are most consistent seems to be: prematurity, chronologic age (age <3 months), chronic lung disease of prematurity, congenital heart disease, birth relative to the RSV season, child care attendance and young children living in the home. Male gender, breast feeding <2 months, family history of wheezing (some studies have found history of atopy to be protective), crowded household and passive exposure to cigarette smoke are scientifically unsound and would include almost the entire birth cohort.

Your view of the balance of desirable and undesirable consequences of the intervention	No	Probably not	Don't know	Probably	Yes
	Undesirable consequences clearly outweigh desirable consequences	Undesirable consequences probably outweigh desirable consequences	Consequences equally balanced or uncertain	Desirable consequences probably outweigh undesirable consequences	Desirable consequences clearly outweigh undesirable consequences
Decision	**Do not cover**	**Coverage with evidence development**		**Cover**	
Restriction (any restriction to the introduction of the option/intervention in the specific setting)					
Justification (reason for deciding the intervention should be covered, covered with evidence development or not covered)					
Implementation (details regarding the decision, including any restrictions on coverage and conditions for coverage with evidence development)					

References

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Framework for going from evidence to a coverage decision

Questions

1. Should robotic-assisted minimally invasive radical prostatectomy (using already purchased robots) be covered versus open surgery (the current standard)?
2. Should new robots be purchased for robotic-assisted minimally invasive radical prostatectomy?

Background Information

Robotic-assisted radical prostatectomy is being proposed and used as a minimally invasive technique for surgeries requiring a very high degree of precision due to the small size of the surgical site as well as the relevance of the reconstruction phase.

In Emilia Romagna Region there are two robots in two hospitals.

The increase in prostate-specific antigen (PSA) screening, combined with a reduction in threshold of indications for biopsy has contributed to an increase in the diagnosis of prostate cancer and consequently to an increase in the number of candidates for radical prostatectomy. In Emilia Romagna in 2007 a total of 1900 prostatectomies were performed: 96% were open surgery and only the 4% were laparoscopic (not robotic-assisted).

Criteria	Evidence	Judgement
Seriousness of the condition Is the condition severe (e.g. life threatening or disabling)?	Radical prostatectomy is associated with complications including intraoperative blood loss, postoperative urinary incontinence and erectile dysfunction.	Yes ☐ Uncertain ☐ No ☐
Quality of evidence Can we be confident in the estimates of effect?	Up to now the effects of robotic-assisted minimally invasive radical prostatectomy have only been evaluated in observational studies with short-term follow-up and important limitations.	Yes ☐ Uncertain ☐ No ☐
Benefits Are the desirable effects large?	It is uncertain whether robotic-assisted minimally invasive radical prostatectomy reduces mortality, recurrence (as measured by positive surgical margins), the need for transfusions, or the risk of incontinence or erectile dysfunction length of hospital say	Yes ☐ Uncertain ☐ No ☐
Adverse effects Are the undesirable effects small?	It is uncertain whether robotic-assisted minimally invasive radical prostatectomy increases the risk of complications (incontinence or erectile dysfunction) when done by surgeons with limited experience	Yes ☐ Uncertain ☐ No ☐
Resource use (costs) Are the resources required (costs) small?	**Costs per intervention (€)** **Robo ic / Laparoscopic** Purchasing 5.600 / 170 Maintenance 2.100 / 10 Robot Consumable 1.800 / 0 Doctors 900 / 1170 Nurses 350 / 455 Materials 1.000 / 1200 Surgical room 450 / 450 Diagnostic-laboratory 50 / 50 Overheads 1.850 / 525 **Total costs 14.100 / 4.030**	Yes ☐ Uncertain ☐ No ☐
Cost-effectiveness Is the cost small relative to the net benefits?	No published data available	Yes ☐ Uncertain ☐ No ☐
Feasibility Is it feasible to avoid any administrative constraints and to ensure appropriate use?	- There is limited availability of surgeons currently able to use the robot. - Its use requires surgeons who can supervise surgeons who are learning how to use the robot. - There is a learning curve of at least 150 to 250 cases (with greater volumes associated with better outcome) for surgeons switching from open surgery. - There is uncertainty about long term consequences if the robot is out of service and there no longer are experienced surgeons capable of performing open surgery.	Yes ☐ Uncertain ☐ No ☐
Equity Would inequities be reduced?	The intervention might only be available to those able to pay if it is not covered by insurance.	Yes ☐ Uncertain ☐ No ☐

GRADE DECIDE

Your view of the balance of desirable and undesirable consequences of the intervention	Desirable consequences clearly outweigh undesirable consequences ☐	Desirable consequences probably outweigh undesirable consequences ☐	Consequences equally balanced or uncertain ☐	Undesirable consequences probably outweigh desirable consequences ☐	Undesirable consequences clearly outweigh desirable consequences ☐
Decision on coverage	**Yes** ☐	**Coverage with evidence development** ☐		**No** ☐	
Justification (reason for deciding the intervention should be covered, covered with evidence development or not covered)					
Implementation (details regarding the decision, including any restrictions on coverage and conditions for coverage with evidence development)					