

A common policy framework for evidence generation on promising health technologies

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Background: Generation of additional evidence may be necessary to access new promising technologies (marketing approval or coverage). Access with evidence generation (AEG) is a more recent concept with regard to coverage than to marketing approval.

Objectives: One aim of Work Package 7 (WP7) Strand A of the European network for Health Technology Assessment (EUnetHTA) was to provide an overview of national AEG mechanisms associated with marketing approvals and funding or coverage decisions.

Methods: A systematic literature review, surveys of WP7 Partners, and consultation of key people were used to obtain information on the AEG mechanisms used by twenty-three countries (twenty European countries, United States, Canada [Ontario], and Australia).

Results: Interest in the implementation of AEG policies, particularly at the coverage decision stage, is growing. An overview of national experiences was used to draw up a generally applicable five-step policy framework for AEG mechanisms that comprised (i) a first assessment identifying knowledge gaps; (ii) a decision conditional to evidence generation; (iii) generation of the evidence requested; (iv) re-assessment integrating the new evidence; (v) a revised decision. The critical factors for success that were identified were coordination, methodological guidance, funding, and a regulatory framework. Countries were categorized on the basis of current implementation of the proposed policy framework.

Conclusions: International collaboration is necessary to gather a critical mass of high-quality data quickly and to ensure timely access to new promising technologies. The overview produced by WP7A has led to development of tools to facilitate collaboration on evidence generation.

Keywords: Health technology assessment, Evidence-based decision making, Conditional coverage, Conditional marketing approval

Access to new health technologies is subject to many constraints in most developed countries because these technologies are often costly and their impact on health and the health-care system is uncertain. Obtaining marketing approval for

a health product (medicine or medical device) requires, in addition to quality assurance data, evidence on safety and efficacy, mostly collected in controlled settings and according to clearly defined standards (e.g., randomized controlled trials, RCT). However, to obtain coverage or funding for health technologies (medicines, medical devices, and diagnostic, medical, and surgical procedures), evidence on clinical effectiveness is often mandatory and may even need to be substantial. Additional data on quality of life, cost-effectiveness, and impact (e.g., on organization of care) may also be requested. All this further evidence is often collected in real-world,

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pragmatic studies that might not be in the standard form of an RCT and for which no international guidance exists (36).

A major obstacle to ensuring timely access to new health technologies is inadequate evidence on which to base the decision to market or provide coverage, especially if the technology is highly innovative or “promising” (36). Manufacturers, clinicians, and patient groups put pressure on decision makers. They demand early decisions and rapid access, but this increases the risk of inappropriate decisions. The authorities may unduly delay potential benefits to patients by waiting for stronger evidence, or may endorse technologies that later turn out to have a low benefit-risk ratio, to be ineffective, cost-ineffective, or even harmful (36).

Hence, Several countries have therefore developed policy frameworks and mechanisms that allow temporary access to promising technologies while concurrently requesting the generation of additional evidence to reduce uncertainty. We refer to these mechanisms as *access with evidence generation* (AEG). Their objective is an optimal trade-off between stakeholders’ needs, flexibility, responsiveness, and rigor. The decision to provide access is revised when the new evidence becomes available (33;35).

OBJECTIVES

The aim was to identify the AEG mechanisms implemented in various countries, to use them to draw up a common policy framework applicable at both the marketing approval and coverage decision stages, and to identify the key factors for its successful operation.

METHODS

Development of the Common Policy Framework

A draft version of the common policy framework was developed on the basis of a review of the literature on AEG mechanisms and a survey of WP7A Partners (Supplementary Table 1, which is available at www.journals.cambridge.org/thc2009003). A search was made for publications on AEG mechanisms (Databases: MEDLINE, BIOSIS Previews, Current Contents, EMBASE, INAHTA and DARE; period: 1990–2008; languages: English or French) using four systematic search strategies (18). Additional information was obtained from the gray literature (reports on the Web sites of medicines agencies, HTA agencies and national health insurance bodies). The survey attempted to identify the AEG mechanisms in use in Europe (response rate: 93%). This draft was discussed among WP7A partners, after attending key conferences and interviewing people working in the field. It was amended in the light of the comments. A second survey was performed to identify those countries that implemented the proposed policy framework in part or in full (response rate: 34%).

Excluded Topics

The following were excluded:

- (i) Early warning and horizon scanning systems: Their purpose is to identify and inform policy makers on forthcoming new health technologies and to help prioritize HTA. There is no prospective data collection (19).
- (ii) Investigational use of nonapproved medical devices or medicines with data collected in clinical trials requested by the regulatory bodies and funded by the applicant: This was considered to be part of the conventional procedure for obtaining marketing approval or licensing, for example, Australia (5) and the United States (22).
- (iii) Compassionate use of health technologies: Specific groups of individuals (e.g., with rare diseases) can often obtain rapid access to innovative technologies. This does not, however, usually require data collection (3;40;49).
- (iv) Special authorization for use of unapproved medicines: This provides patients with temporary access to medicines that are not yet available in the country, or that are still under development, that is, before marketing authorization. It may be granted in France (Temporary Authorization for use—“Cohort ATU”) (1) and Italy (*Uso terapeutico di medicinale sottoposto a sperimentazione clinica*) (40) for medicines used to treat serious or rare diseases for which alternative treatments are not available and for which preliminary evidence strongly suggests a positive benefit/risk ratio. This mechanism focuses more on enabling early access than on collecting evidence and cannot replace investigational clinical trials.
- (v) “Routine” vigilance systems (15) for medicines and devices: These are based on spontaneous reporting of data. Data collection is neither systematic nor comprehensive (36).

RESULTS

AEG mechanisms are used when two important decisions are made during a technology’s life cycle: (i) marketing approval and (ii) coverage.

AEG Mechanisms Associated With Marketing Approval Decisions

Medicines. We identified not only the AEG mechanisms recommended by the European Medicines Agency (EMA), applicable to European Union (EU) countries and implemented by the European Commission (EC), but also country-specific mechanisms (in fourteen of twenty-three countries: Australia, Belgium, Canada, Denmark, Finland, France, Germany, Italy, Latvia, Netherlands, Portugal, Spain, United States, and United Kingdom). Overall, they fell into two categories: (i) conditional marketing authorization and (ii) postmarketing studies (Supplementary Table 2, which is available at www.journals.cambridge.org/thc2009003).

Conditional Marketing Authorization. The EC may grant conditional marketing authorization when the

new medicines have orphan status, or are intended for seriously debilitating, life-threatening diseases or emergency situations (e.g., pandemics). At least four conditions must be met: (i) preliminary evidence should indicate a positive benefit/risk ratio; (ii) the applicant should be able to provide comprehensive data; (iii) unmet medical needs should be fulfilled; (iv) the public health benefit of immediate access should outweigh the risk due to uncertainty. The decision is made before comprehensive clinical data becomes available. Authorization is granted on a yearly basis and carries the legal obligation to provide further evidence on safety and efficacy (completion or initiation of studies). Conventional marketing authorization may be granted after yearly review of the evidence generated (16).

Some countries also have their own conditional marketing authorization mechanisms, for example, Italy (*Autorizzazione subordinata a condizioni*) (41), Spain (*Autorización especial*) (3), Denmark (37), Germany (20), Belgium (46), and Canada (Notice of compliance with conditions: NOC/c) (50).

Postmarketing Studies (Including Active Pharmacovigilance). Postmarketing studies are not a prerequisite to marketing approval, but the data collected (e.g., on safety or efficacy in a given population in the usual clinical setting) may impact at any time on the benefit/risk ratio and thus result in changes to marketing authorization (Supplementary Table 2) (17). Most postmarketing studies address safety concerns, as data on safety tends to be limited when approval is granted. Proactive actions to complement routine pharmacovigilance systems (spontaneous reporting of adverse events) are now implemented worldwide.

In the EU, whenever safety concerns arise during clinical trial assessments, the EMEA requests further data collection and appropriate pharmacovigilance, with quantification of adverse events (15). Some Member States implement additional active surveillance to meet their own specific needs: Belgium (46), Finland (44), France (2), Germany (20), Italy (41), Latvia (29), Netherlands (11), Portugal (33), Spain (39), and the United Kingdom (21). This also occurs in Australia (6) and the United States (23).

Medical Devices. Much less information was found on medical devices than on medicines. Two types of AEG mechanisms for marketing approval were identified in seven of twenty-three countries (Australia, Canada, Latvia, Spain, Switzerland, United States, and United Kingdom): (i) conditional licensing and (ii) postmarketing clinical follow-up.

Conditional Licensing. Conditional licensing may be granted to new moderate- or high-risk medical devices in Canada “when there is reasonable assurance that the device is safe and effective but supplemental information is required to support this conclusion” (49). The applicant has to fund and set up studies to collect additional clinical data to confirm the benefit/risk ratio within a set deadline (49).

Postmarketing Clinical Follow-up (or Postapproval Surveillance). Several follow-up methods are available (24;28;56): long-term surveillance of the patients who were included in preapproval clinical trials, prospective observational studies, registries, or new clinical trials. The Global Harmonization Task Force (GHTF) has performed extensive work on regulatory approaches about postmarketing surveillance and clinical assessment of medical devices and has proposed guidance (25;26). Funding comes from either the holder of the marketing approval or public institutions.

A new EU directive applicable from March 2010 (13) will request systematic data collection during postmarketing surveillance (unless nonapplicability can be justified). This follows the guidance issued by the Medical Devices Evaluation Committee (MEDDEV) (14) – already implemented by Latvia (29) and Switzerland (52).

AEG Mechanisms Associated With Coverage Decisions

AEG mechanisms associated with coverage decisions, unlike those associated with marketing approval are recent. To date, few countries have implemented such mechanisms (10;32;45;55), but an increasing number are showing interest and attempting to identify mechanisms that will meet their local needs and constraints. These mechanisms are applied to medicines, medical devices, and/or procedures (Table 1). We identified only twelve of twenty-three countries implementing AEG mechanisms before coverage decisions: Canada (Ontario) (42;43;47), Spain (38), Australia (43), United States (55), Switzerland (12), Sweden (53), Belgium (9), Netherlands (51), France (27), England/Wales (10;45), Germany (10), and Italy (4).

The mechanisms fell into three main categories of uncertainty: (i) the “No, unless . . .” category which considers that evidence is inadequate to grant coverage unless additional requirements are met; (ii) the “Yes, but . . .” category which considers that the evidence is reasonably adequate to grant coverage provided that additional evidence is generated, and (iii) the “Yes for now” category which considers that the evidence is adequate to grant standard coverage but requests data on specific points (e.g., on conditions of use). Access may be limited to patients included in a clinical trial or treated in data collection centers, or may be unrestricted. Tables 1 and 2 show the AEG mechanisms implemented by each category and the bodies involved.

Some countries (Canada [Ontario], Spain, Australia, United States, Switzerland, Sweden, Belgium, Netherlands, France, and England/Wales) implement a structured form of AEG (conditional coverage) which is usually part of an established policy framework, in which the initial decision on coverage is conditional to the generation of evidence in response to the decision-makers’ requests (10;32;55). Data are collected prospectively under experimental conditions

Table 1. Main Characteristics of AEG Mechanisms Associated with Coverage Decisions

AEG system (Name, country)	Health technologies concerned	Type of initial decision	Requirement for AEG decision	Examples
Only in research (England/Wales)	Medicines, medical devices, interventional procedures, and public health interventions	“No, unless. . .”	The use of a promising technology or a public health intervention is not supported by enough robust evidence	<ul style="list-style-type: none"> - Laparoscopic surgery for colorectal cancer - Taxanes as adjuvant in early node positive breast cancer - Verteporfin in ARMD. . .
Suspended coverage decision with pilot project (Germany)	Medical devices within a procedure	“No, unless. . .”	Not enough evidence to conclude on the benefit, necessity, or efficiency	<ul style="list-style-type: none"> - Acupuncture for chronic pain - Screening for skin cancer - Balneo-phototherapy. . .
Conditionally funded field evaluation (Canada, Ontario)	Medicines, medical devices, procedures, and public health interventions	“Yes, but. . .”	<ul style="list-style-type: none"> - Uncertainty (low quality of evidence) about effectiveness, cost-effectiveness, or safety - Need for quality controls prior to unrestricted diffusion - Potential disruptive effects - Large potential investment 	<ul style="list-style-type: none"> - PET scanners - Endovascular treatment of abdominal aneurysms - Drug eluting stents - Surgical treatment of epilepsy - Cardiac CT angiography. . .
Monitored use (Spain)	Medical devices, medical and surgical procedures	“Yes, but. . .”	Uncertainty about effectiveness and safety at the initial coverage decision stage	<ul style="list-style-type: none"> - Surgical treatment of epilepsy - PET scanners - Endovascular treatment of abdominal aneurysms. . .
Interim funding (Australia)	Medical devices, medical and surgical procedures	“Yes, but. . .”	For promising technologies which are (i) safe, effective but with uncertain cost-effectiveness or (ii) with uncertain effectiveness and safety but potent cost-effectiveness	<ul style="list-style-type: none"> - PET scanners - Deep-brain stimulators - Endovascular treatment of abdominal aneurysms. . .
Coverage with evidence development (CMS) (US)	Medicines, medical devices, medical and surgical procedures	“Yes, but. . .”	Evidence complementary to existing medical evidence is required on effectiveness, safety or cost-effectiveness	<ul style="list-style-type: none"> - Lung volume reduction surgery - Cochlear implants - Implantable cardioverter defibrillators - PET scanners. . .
Medical service under evaluation (Switzerland)	Controversial procedures	“Yes, but. . .”	Uncertainty about effectiveness and safety at the initial coverage decision stage	<ul style="list-style-type: none"> - Bariatric surgery - Surgical treatment of epilepsy - Curietherapy in prostate cancer - Intervertebral disc replacement - Verteporfin in ARMD. . .
Reimbursement with conditions (Sweden)	Innovative medicines	“Yes, but. . .”	Uncertainty about effectiveness, safety, cost-effectiveness, or conditions of use	<ul style="list-style-type: none"> - Diabetes and weight loss treatment - Cancer drugs and biologicals. . .
Conditional reimbursement (Belgium)	Innovative implants	“Yes, but. . .”	Uncertainty about effectiveness, safety, or condition of use	<ul style="list-style-type: none"> - Deep brain stimulation - Endovascular treatment of abdominal aneurysms - Drug eluting stents for diabetic patients - Contralateral cochlear implant. . .

Table 1. Continued

AEG system (Name, country)	Health technologies concerned	Type of initial decision	Requirement for AEG decision	Examples
Conditional reimbursement (Netherlands)	Hospital prescribed medicines (e.g., costly or orphan medicines)	“Yes, but . . .”	Uncertainty regarding relative therapeutic value, relative cost-effectiveness, and importance to public health	-Bevacizumab, -Trastuzumab, -Anidulafungin. . .
Still in clinical research (France)	Medical and surgical procedures	“Yes, but . . .”	Clinical benefit cannot be fully established	- Intensity-modulated radiation therapy ^a - Extracranial stereotactic radiotherapy ^a - Biochemical markers of liver fibrosis ^a . . .
Post-listing studies (France)	Medicines and medical devices	“Yes for now. . .”	Uncertainty on conditions of use, safety, impact on organization of healthcare. . .	- IFN- β - Anti TNF- α medicines - Transcutaneous implanted pulmonary valve. . .
Independent research on medicines (Italy)	Medicines, public health interventions	“Yes for now. . .”	- Rare diseases; - High impact in terms of public health or economy; - Long-term safety during treatment of chronic diseases. . .	- IFN- β vs azathioprine - Bevacizumab - Evaluation of impact of educational interventions of patient with psoriasis. . .

^aRecommended by national HTA agency, but no data generated.

AEG, Access with Evidence Generation; ARMD, age-related macular degeneration; PET, positron emission tomography; CT, computed tomography; IFN, interferon; TNF, tumor necrosis factor.

(clinical trials) or under real-life conditions (registries, observational, pragmatic, or health economics studies). Their results are taken into account in the reassessment and in the subsequent revised coverage decision (10;32;55) that may lead to standard coverage, modification of coverage conditions, or even to delisting.

Table 3 compares the strengths and weaknesses of all these AEG mechanisms.

Common Policy Framework for AEG Mechanisms

The above descriptions of the AEG mechanisms currently implemented, whether for marketing approval or coverage/reimbursement decisions, were used to construct a *common-denominator* model underlying a five-step policy framework (Supplementary Figure 1, which is available at www.journals.cambridge.org/thc2009003):

Step 1. A first assessment pinpoints evidence gaps and data needs and proposes a plan for data collection (type of data and study, time period, etc.).

Step 2. A decision is made on conditional and temporary access to the technology. This decision is based on the first assessment and is accompanied by a request for evidence generation (which type of data needs to be collected and analyzed to fill which evidence gaps, in reply to which uncertainties voiced by the decision makers).

Step 3. During an interim period of conditional access to the technology, the data that have been requested are collected and the use of the technology is monitored. Conditions of use are usually restricted and well-defined (e.g., in a limited number of centers, performed by highly skilled professionals, etc.).

Step 4. A second assessment that includes the new evidence is performed.

Step 5. A revised decision based on this second assessment is made with regard to access to the technology.

Outcomes of this process may be widespread and appropriate availability of the technology, restricted diffusion, or discontinuation of use.

During construction of the model, WP7A Partners drew attention to the reported barriers against establishing and operating a completely operational system at the coverage stage (10;32;55) and stressed the need to establish critical success factors (Box 1).

This common policy framework and associated critical success factors apply to the implementation of AEG both at the marketing approval and coverage decision stages. It is derived from the current regulatory framework for medicines. Although all five steps and all factors are usually applied in the case of medicines (EMA has defined study designs, quality requirements, organized the coordination of bodies, etc.), many steps and factors are often omitted in the case of coverage decisions (Table 3).

Table 2. Role of Identified Collaborators in AEG Mechanisms Associated with Coverage Decisions

AEG system (Name, country)	Coordinating structure	Source of funding for data collection ^a	Structure performing data collection	Structure performing data analysis	Decision-making authority
Only in research (England/Wales)	NICE	-Public (NHS R&D, MRC. . .) -Private (manufacturers. . .)	Various partners (health professionals, manufacturers. . .)	Various partners (health professionals, manufacturers. . .)	NICE
Suspended coverage decision with pilot project (Germany)	Statutory Health Insurance/ Association of statutory health physicians	- Public (Statutory Health Insurance)	Health professionals (mostly the Association of statutory health physicians)	Not determined	GB-A
Conditionally funded field evaluation (Canada, Ontario)	OHTAC/MAS	Public (Ministry of Health and long-term care)	PATH, THETA, other academic partners, research organizations	PATH, THETA, other academic partners	Ministry of Health and long-term care
Monitored use (Spain)	National Health Service's Interterritorial Council	Public (Ministry of Health)	Public hospitals	HTA agencies (AETS, AETSA, Avalia-t. . .)	Ministry of Health
Interim funding (Australia)	MSAC	Public (Ministry of Health and aging)	Associations of health professionals	Associations of health professionals	Ministry of Health and aging
Coverage with evidence development (CMS) (US)	CMS	Mostly public (CMS for clinical costs only, stakeholders for other costs. . .)	Various partners (institutions, health professionals. . .)	Various partners (institutions, health professionals. . .)	CMS
Medical service under evaluation (Switzerland)	Federal Office of Public Health	Mostly public (Sickness Funds or applicants)	Applicant (health professionals, manufacturers)	Not determined	Federal Department of Home Affairs (advised by ELK)
Reimbursement with conditions (Sweden)	TLV	Manufacturers	Manufacturers	TLV	TLV
Conditional reimbursement (Belgium)	KCE/INAMI	Public (INAMI)	Health professionals	KCE/INAMI	INAMI
Conditional reimbursement (Netherlands)	CVZ	Manufacturers/ ZonMW	Various partners (Manufacturers, health professionals, academic partners, institutions. . .)	CVZ	Ministry of Health, Welfare and Sport
Still in clinical research (France)	HAS	UNCAM for clinical costs only; currently no funding for other costs	Health professionals	HAS	HAS/UNCAM
Post-listing studies (France)	HAS	Manufacturers	Manufacturers	Manufacturers	Ministry of Health
Independent research on medicines (Italy)	AIFA	Public (AIFA)	Health professionals	AIFA	Regional institutions

^a Funding may not be systematically guaranteed.

AETS, Spanish National Health Technologies Assessment Agency; AETSA, Andalusian Health Technologies Assessment Agency; AIFA, Italian Medicine Agency; Avalia-t, Galician Health Technologies Assessment Agency; CMS, American Center for Medicare/Medicaid services; CVZ, Dutch Health care insurance board; ELK, Swiss Federal Commission for general health insurance benefits; GB-A, German Federal-joint Committee; HAS, French High Authority for health; INAMI, Belgian National Health Insurance; KCE, Belgian Healthcare Knowledge Center; MAS, Medical Advisory Secretariat (Ontario); MRC, British Medical Research Council; MSAC, Australian Medical Services Advisory Committee; NHS, British National Health Services; NICE, National Institute for Health and Clinical Excellence; OHTAC, Ontario Health Technology Advisory Committee; Osteba, Basque Office for Health Technology Assessment; PATH, Program for the Assessment of Technologies in Health (Ontario); THETA, Toronto Health Economics and Technology Assessment Collaborative; TLV, Swedish Dental and Pharmaceutical Benefits Agency; UNCAM, French National Health Insurance; ZonMW, Netherlands organization for Health Research and Development.

Table 3. Reported Strengths and Weaknesses of AEG Systems at the Coverage Stage

AEG system (Name, country)	Reported strengths	Reported weaknesses
Only in research (England/Wales)	<ul style="list-style-type: none"> - Regulatory framework - Methodological guidance 	<ul style="list-style-type: none"> - No dedicated funding - No systematic collaboration between partners - Not a systematic process (opportunistic)
Suspended coverage decision with pilot project (Germany)	<ul style="list-style-type: none"> - Dedicated funding^a 	<ul style="list-style-type: none"> - Incomplete regulatory framework as regards project implementation and use of results in decision making - For medical devices used as part of a procedure only - No methodological guidance - No systematic collaboration
Conditionally funded field evaluation (Canada, Ontario)	<ul style="list-style-type: none"> - Dedicated funding^a - Systematic collaboration between partners - Regulatory framework - Methodological guidance - Operational system - Great way to engage end users. 	<ul style="list-style-type: none"> - High pressure - Regional system (limited to Ontario)
Monitored use (Spain)	<ul style="list-style-type: none"> - Dedicated funding^a - Systematic collaboration between partners - Regulatory framework - Methodological guidance - Operational system 	<ul style="list-style-type: none"> - No selection criteria for technologies to be monitored
Interim funding (Australia)	<ul style="list-style-type: none"> - Dedicated funding^a - Regulatory framework - Methodological guidance - Operational system. 	<ul style="list-style-type: none"> - For medical devices and procedures only - No systematic collaboration between partners - Funding (MBS) not fully adapted to “interim funding” - Trial duration too long (>3 yr) for conditional coverage - National target populations too small; interim funding while awaiting results of international studies
Coverage with evidence development (CMS) (US)	<ul style="list-style-type: none"> - Regulatory framework - Methodological guidance (partial) 	<ul style="list-style-type: none"> - No dedicated global funding - No systematic collaboration between partners - Not a systematic process (opportunistic) - Difficulties in designing CED studies
Medical service under evaluation (Switzerland)	<ul style="list-style-type: none"> - Regulatory framework - Dedicated funding^a - Operational system 	<ul style="list-style-type: none"> - For controversial medical procedures only - No systematic collaboration (depends on applicant) - Constraints of public administration human and financial resources
Reimbursement with conditions (Sweden)	<ul style="list-style-type: none"> - Regulatory framework - Dedicated funding^a - Mandatory engagement of manufacturer - Operational system 	<ul style="list-style-type: none"> - For innovative drugs only - Difficulties in interpreting observational studies - Difficulties with effectiveness studies
Conditional reimbursement (Belgium)	<ul style="list-style-type: none"> - Regulatory framework^b - Dedicated funding^a - Collaboration between partners - Operational system 	<ul style="list-style-type: none"> - For innovative new implants only
Conditional reimbursement (Netherlands)	<ul style="list-style-type: none"> - Regulatory framework - Dedicated funding^a - Mandatory engagement of manufacturer 	<ul style="list-style-type: none"> - For hospital-prescribed medicines (costly or orphan medicines) only
Still in clinical research (France)	<ul style="list-style-type: none"> - Regulatory framework^b 	<ul style="list-style-type: none"> - For medical and surgical procedures only - No dedicated global funding - No collaboration between partners - No operational system.
Post-listing studies (France)	<ul style="list-style-type: none"> - Dedicated funding^a (by the manufacturers) - Regulatory framework - Methodological guidance - Mandatory engagement of manufacturer 	<ul style="list-style-type: none"> - For medicines and medical devices only - Difficulties to find agreement on study design - No conditional or temporary coverage (but linked with strict conditions).
Independent research on medicines (Italy)	<ul style="list-style-type: none"> - Implemented regulatory framework - Dedicated funding^a - Methodological guidance 	<ul style="list-style-type: none"> - For medicines only - No systematic collaboration (research projects only) - No conditional or temporary coverage

^aDedicated funding may not be systematically guaranteed.

^bA change in the law on innovative technologies has been proposed to achieve a more operational mechanism.

Table 4. Degree of Implementation of AEG Mechanisms by Various Countries

Country	Marketing approval		Coverage decision		
	Medicine	Medical device	Medicine	Medical device	Procedure
Canada (Ontario)	+++ ^N	+++	+++	+++	+++
Spain	+++ ^{E,N}	+++	+++	+++	+++
Australia	+++ ^N	+++	+++/ ⁺	+++	+++
US	+++ ^N	+++	+++	+++	+++
England/Wales	+++ ^{E,N}	++	+++	+++	+++
France	+++ ^{E,N}	++	+++	+++	++/+
Germany	+++ ^{E,N}	++	++	+++/ ⁺	++
Sweden	+++ ^E	–	+++	++	++
Belgium	+++ ^{E,N}	–	–	+++	–
Italy	+++ ^{E,N}	–	+++/ ⁺	+/-	+/-
Netherlands	+++ ^{E,N}	–	+++/-	–	–
Switzerland	–	+++	–	–	+++/-
Austria	+++ ^E	–	++	++	++
Denmark	+++ ^{E,N}	–	++	++	++
Latvia	+++ ^{E,N}	+++	–	–	–
Portugal	+++ ^{E,N}	–	–	–	–
Finland	+++ ^{E,N}	–	–	–	–
Poland	+++ ^E	–	–	–	–
Ireland	+++ ^E	–	–	–	–
Estonia	+++ ^E	–	–	–	–
Slovenia	+++ ^E	–	–	–	–
Cyprus	+++ ^E	–	–	–	–
Norway	–	–	–	–	–

Note. +++, full AEG; ++, partial AEG; +, passive AEG; –, No AEG. ^E, AEG implemented by EMEA and applicable in European Countries; ^N, country-specific AEG implemented at national level.

Box 1. Barriers to and Critical Success Factors for Evidence Generation

Barriers	Critical success factors
<ul style="list-style-type: none"> • Difficulty in agreeing on data requirements and study design • Evidence generated does not meet quality criteria and cannot therefore inform a decision • Lack of coordination among the Partners and bodies overseeing data collection • Limited funds to finance the generation of evidence that meets HTA agency and decision-maker requirements • No well-defined regulatory framework governing coordination and financing 	<ul style="list-style-type: none"> • Coordinating body overseeing the contributions and collaboration of all participants • Scientific leadership and clear guidance on key methodological issues (e.g., study design) for relevant and high-quality evidence • Dedicated funding for data collection and analysis (e.g., studies and registries), regardless of source • Regulatory framework

Ranking Implementation of AEG Mechanisms

We compared our observations on the implementation of AEG mechanisms with the model policy framework. To do this, we arbitrarily defined four levels of execution:

- (i) **Full implementation:** All five steps and all four critical success factors are implemented. The first assessment identifies evidence gaps. Data collection meets quality standards. The revised decision is based on an updated literature review and on the additional data generated.
- (ii) **Partial implementation:** The five steps are fully operational. The first assessment identifies evidence gaps. However, data collection is hampered by national constraints on implementation of the success factors. The revised decision is based on

an updated literature review, but on partial data collection only (mostly registry data).

- (iii) **Passive implementation:** The first assessment identifies evidence gaps, but data are not collected usually for financial or regulatory reasons. The revised decision is based on an updated literature review only.
- (iv) **No implementation:** There is no systematic identification of new technologies nor any follow-up of their diffusion. No second assessment is performed.

As illustrated in Table 4, the degree of implementation (full, partial, passive, or absent) varied widely among the twenty-three countries.

DISCUSSION

Timely access to new promising technologies (marketing approval or coverage) often depends on the generation of additional evidence (36). Access with evidence generation (AEG) is well known in the context of marketing approval, but is a more recent concept in relation to coverage (10;32;55). Few countries have experience of AEG as applied to coverage. The issue has been hotly debated by WP7A and also by the Health Technology Assessment international (HTAi) special interest group on “conditional coverage and evidence development for promising technologies” (30).

WP7A reviewed the national AEG mechanisms associated with coverage decisions using the gray literature (Web sites informing on local laws, regulatory frameworks, and procedures), interviews, and surveys of WP7A Partners, as published data was scarce especially for Europe. The review may have shortcomings, but it has served its purpose of informing a debate among WP7A Partners to move toward international collaboration.

Coverage decisions were linked to AEG mechanisms in ten of the twenty-three countries studied (Canada [Ontario], Spain, Australia, United States, Netherlands, Sweden, Switzerland, England/Wales, France, and Germany) (10;32;55). In most of these countries, requests for AEG filled knowledge gaps and enabled decisions on the appropriate diffusion of several promising technologies after conditional coverage, for example, lung volume reduction surgery (United States), positron emission tomography scanning (Canada, Australia, Spain, United States), and endovascular repair of abdominal aneurysms (Canada, Australia, Spain). However, the system does not always work. For instance, no funding could be found for evidence generation on cochlear implants in the United States, and the lack of meaningful endpoints for implantable cardioverter defibrillators (ICD) meant that American ICD register results were disappointing and of no use (54).

We used the review to construct a five-step model policy framework for AEG mechanisms for implementation and/or adaptation by interested countries. This framework, together with its critical success factors, covers new and existing conditional coverage frameworks and includes relevant adaptations from the long-standing regulatory frameworks for medicines. It is thus applicable to AEG at the marketing approval stage (where all 5 steps are implemented) and at the coverage decision stage (where steps are often omitted). The framework revolved around the collection of relevant data on promising technologies that could effectively support decisions on appropriate diffusion or discontinuation of use. However, the actions needed to generate these data may require changes to currently applicable policy frameworks.

The critical success factors that were identified were (i) coordination, (ii) methodological guidance, (iii) funding, and (iv) an implemented regulatory framework. Their absence can hamper data collection.

- (i) A named body should coordinate all actions. For instance, in Spain and Canada, decision makers, HTA organizations, healthcare professionals, and researchers cooperate to garner data and implement policy recommendations under the supervision of a coordinating body. In contrast, in the French system of conditional coverage for medical and surgical procedures, coordination between the Ministry of Health, national health insurance, the HTA agency, health professionals, and industry has been poor despite each stakeholder's interest, partly because of the lack of a suitable funding mechanism. Hopefully, a scheduled change in the law on innovative technologies will lead to improvements. In the case of medicines, collaboration is needed between the regulatory setting (assessment and marketing decision) and the HTA setting (assessment and coverage decision) to avoid duplication of work (e.g., between national medicine agencies and HTA agencies). Assessment reports from the marketing authorization process or postmarketing data may also be useful in an initial HTA.
- (ii) There must be clear scientific guidance to define precisely the most appropriate type of data and study design to ensure that evidence will ultimately improve. The timeliness and duration of data collection are also important, although there is no consensus on criteria to determine duration (32;54).
- (iii) Dedicated financing mechanisms for data collection and analysis are essential, especially before deciding on coverage. Funding should be adequate so that data collection does not end prematurely, or result in generating low-quality data. It could be restricted to data collection in certain centers only. There might be just a single source of funding (generally public) or multiple sources (public, private, or mixed), often each covering a specific cost. For example, the National Heart Lung and Blood Institute (NHLBI) supported the funding and administration of the National Emphysema Treatment Trial (NETT), whereas Centers for Medicare/Medicaid Services (CMS) paid for patient care (8). Opportunity for public-private partnership should also be considered (7).
- (iv) A regulatory framework should clearly state the role and responsibility of each Partner and ensure that the AEG results are used during the revised decision process. For instance, in Germany, the results from pilot projects are not systematically considered during reassessment because of lack of a regulatory framework.

Other challenging issues concerning promising health technologies, and not listed among the above success factors are: (i) collaboration with academic research, (ii) uncertainty thresholds, selection and prioritization, (iii) timing of the request for evidence generation, and (iv) the relationship between HTA and AEG.

- (i) Decisions on conditional access are usually made independently of decisions on clinical research. We noted that AEG mechanisms were strengthened when HTA agencies, decision makers, and research institutions collaborate, as in Ontario.
- (ii) The criteria for estimating uncertainty and prioritizing technologies that might benefit from an AEG mechanism should be explicit, especially as resources are limited (54;55).

- (iii) When an authority should request evidence generation is a moot point. The trend is toward providing scientific advice in the early stages of the technology's development, as some medicines agencies already do.
- (iv) The initial HTA should clearly quantify uncertainty, identify knowledge gaps and data needs, and indicate avenues for further research with possibly clear guidance on which data should be collected in which type of study to ensure that the evidence generated will meet requirements.

Broader subjects of debate are how the generation of new evidence within AEG fits with clinical research and the ethics of access to technologies for which uncertainties remain. Interest in AEG policies for coverage decisions is growing in Europe as illustrated by the work carried out by EUnetHTA WP7A (twenty countries), but also worldwide as demonstrated by the creation of the HTAi interest subgroup on conditional coverage after the 2008 HTAi meeting (30). International collaboration offers shared methodological expertise, pooled resources, possible harmonization of evidence requirements (31), less duplication, and more HTAs. It would also enable a critical mass of data to be gathered within a reasonable timeframe, especially on health technologies that concern few patients and involve long follow-ups. As a first step toward international collaboration, WP7A has developed tools for evidence sharing on promising technologies (48).

CONCLUSION

Interest in the implementation of AEG policies is growing. WP7A analyzed national experiences and has proposed a general policy framework. The main steps and key factors needed to generate relevant evidence on promising technologies were identified, and the issues they raise were discussed. International collaboration is useful, even necessary, to gather a critical mass of high-quality data quickly, while ensuring timely access to promising health technologies. The work carried out by WP7A has led to the development of tools to facilitate collaboration on evidence generation.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
 Supplementary Table 2
 Supplementary Figure 1
www.journals.cambridge.org/thc2009003

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