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EAES recommendations on methodology of innovation management in endoscopic surgery

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Abstract
Background Under the mandate of the European Association for Endoscopic Surgery (EAES) a guideline on methodology of innovation management in endoscopic surgery has been developed. The primary focus of this guideline is patient safety, efficacy, and effectiveness.
Methods An international expert panel was invited to develop recommendations for the assessment and introduction of surgical innovations. A consensus development conference (CDC) took place in May 2009 using the method of a nominal group process (NGP). The recommendations were presented at the annual EAES congress in Prague, Czech Republic, on June 18th, 2009 for discussion and further input. After further Delphi processes between the experts, the final recommendations were agreed upon.
Results The development and implementation of innovations in surgery are addressed in five sections: (1) definition of an innovation, (2) preclinical and (3) clinical scientific development, (4) scientific approval, and (5)

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This study is conducted by all the authors on behalf of the EAES, and it is also conducted by Gabriela Soskuty on behalf of Eucomed.

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implementation along with monitoring. Within the present guideline each of the sections and several steps are defined, and several recommendations based on available evidence have been agreed within each category. A comprehensive workflow of the different steps is given in an algorithm. In addition, issues of health technology assessment (HTA) serving to estimate efficiency followed by ethical directives are given.

Conclusions Innovations into clinical practice should be introduced with the highest possible grade of safety for the patient (nil nocere: do no harm). The recommendations can contribute to the attainment of this objective without preventing future promising diagnostic and therapeutic innovations in the field of surgery and allied techniques.

Keywords Innovation · Guideline · Surgery · Health technology

At present there is hardly any field of surgery where technical improvements are pushed forward so heavily as in the field of endoscopic surgery. Uncontrolled diffusion of new health technologies in surgery, however, may lead to problems and harm to the patient (e.g., increased complication rates), especially during the introduction of a new technique or technology. It is common sense that *the duty we owe to patients should never be diluted by any other goals.* For the patient, the most important criteria of an innovation are safety, efficacy, and effectiveness.

Hovering over this goal is the underlying principle to support the freedom of science and the freedom of physicians to develop the best possible procedure in order to reach the best obtainable outcome for their patients, reducing the risks and increasing patient safety while undergoing surgical procedures. To achieve such a goal and to ensure a best-practice approach in scientific development as well as in clinical practice, existing standard methodological approaches to evaluate surgical procedures and medical devices should be used in a timely fashion. In addition, limiting legal regulations have to be taken into account. The board of the European Association of Endoscopic Surgery (EAES) felt that evidence-based recommendations were needed for the safe introduction of innovative surgical devices and therapeutic or diagnostic procedures. The resulting guideline should give advice on "when to do what" when implementing innovations in the field of surgery.

Due to technical and medical advances, the field of innovations in medicine is rapidly and continuously growing. Innovations are products of continuous minor or major changes due to surgeon-initiated advances, patient preferences, and improvement of technical facilities. Additionally, they may derive from the medical industry sector involved in research directed toward the development and implementation of new procedures or techniques into surgical practice. The development of surgical practice in the past has mostly been experimental or empirical, and due to the constant need to react to acute and changing conditions related to the need for individual patient care.

A recent publication from the Institute of Medicine in the USA states that:

> decisions that shape the health and health care of Americans—by patients, providers, payers, and policy makers alike—will be grounded on a reliable evidence base, will account appropriately for individual variation in patient needs, and will support the generation of new insights on clinical effectiveness. Evidence is generally considered to be information from clinical experience that has met some established test of validity, and the appropriate standard is determined according to the requirements of the intervention and clinical circumstance. Processes that involve the development and use of evidence should be accessible and transparent to all stakeholders [1].

A model for evidence development in the learning healthcare system by the Institute of Medicine has been published [1].

For pharmaceuticals, strict regulatory procedures exist, aimed to maximize the clinical benefit and to minimize harm to patients. For surgical innovations, however, there are no such rigorous formal regulations. Surgical innovations, especially in the domain of minimal-access surgical interventions, have increased in recent years. Several examples, however, exist where they have been diffused and adopted widely after their feasibility was shown but before sound evidence on safety and/or efficacy had been documented, e.g., increased incidence of iatrogenic biliary injuries [2, 3] in the era of laparoscopic cholecystectomy.

The Helsinki Declaration 2008 [4] (section A, sentences 7 and 8) states:

> The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best current interventions **must** be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality. In medical practice and in medical research, most interventions involve risks and burdens.

In order to improve the safe implementation and evaluation of preventive, diagnostic, and therapeutic interventions (methods, procedures, and treatments) our aim was to develop a guideline with evidence-based clinical practice

recommendations on the methodology of innovation management in the field of endoscopic surgery within the existing formal regulations and requirements. The primary focus is not to hinder innovations, but to introduce innovations into clinical practice with the highest possible grade of safety for the patient (nil nocere: do no harm).

Materials and methods

Constitution of the expert panel

Mandated by the EAES scientific committee, a preliminary literature review was initiated in Cologne. A panel of experts was constituted. Criteria for the selection of experts included (1) clinical and scientific expertise and (2) varied geographical distribution. Special attention was also given to ensure a wide range of expertise. Since the issue of innovations in endoscopic surgery is a multidisciplinary field, representatives of the following fields were asked to participate: surgery, endoscopic gastroenterology, medical ethics, medical device industry (Eucomed), and health technology assessment (HTA agency).

Literature research and critical appraisal

For the literature research we proceeded according to the hierarchy of research evidence. The existing literature on this issue consists to a large extent of expert opinions, congress presentations, editorials, and other "level 5" evidence in the hierarchy of the methodical quality of evidence.

The search for evidence and information included systematic literature research in Medline via Pubmed and the Cochrane Library (method studies, technology assessment, economic evaluations) with the search terms [text words or medical subject headings (MeSH terms)] and strategy: *(Innovat* OR health technol*) AND ("Surgical Procedures, Operative" OR Surger*) AND ("Ethics"OR Ethic* OR "Health Care Economics and Organizations"OR Economic* OR evaluation OR implementation)*, restricted to English- and German-language papers, as well as searching for secondary literature and Internet pages and publications of national medical organizations, the European Commission, and other medical associations/companies ("grey literature," existing guidelines/position statements). Furthermore, the reference lists of retrieved literature were cross-checked for additional studies that might be of relevance.

Critical appraisal of the literature was accomplished as far as possible in terms of coherency of argumentation, stringency, and consistency.

Consensus development and building of the manuscript

After the literature review, a framework of the basic aspects of the subject was constructed by the Cologne group. The resulting document was sent to the members of the expert panel to assess each of these aspects as pertains to relevance for discussion as well as to add any further issues. After analysis of the responses of the expert panel the framework was modified according to the suggestions received, and a preliminary draft of the guidelines was developed.

The first draft was presented to the expert panel a week prior to the consensus development conference (CDC) in Cologne on 15th and 16th May 2009 and was subjected to discussion and modification during the conference. Consensus was sought according to the nominal group process (NGP). If no consensus on single issues could be obtained, this was indicated within the text as a "minority statement."

The strengths of recommendations are expressed by the words "must," "should" or "can" according to the grades of recommendations (GoR) A, B, or C. The degree of consensus was indicated as percentage of agreement by the experts. If a recommendation has a legal foundation, "must" and the GoR A are always used.

During the following month, the statements were reformulated according to expert input then sent out to all members of the expert panel for final approval. At the 17th annual congress of the EAES in Prague, Czech Republic, on June 18th, 2009 the consensus statements were presented to the scientific community for further discussion and input. After further consideration, Delphi processes were initiated to achieve final consensus.

Results

The system of development and implementation of innovations in surgery can be divided into five sections: (1) definition of an innovation, (2) preclinical and (3) clinical scientific development, (4) scientific approval, and (5) implementation and monitoring.

Within the present guideline each of the sections and several steps are defined, the extended algorithm is described in the Appendix. In addition, issues of health technology assessment (HTA) and ethical aspects are discussed.

Definition of innovation

When trying to retrieve definitions of the term "innovation," countless different phrases can be found. The *American Heritage Dictionary* defines "innovation" as (1) the act of introducing something new or (2) something

newly introduced [5]. Since innovations rarely consist of something that is entirely new, the process of innovation most often involves a new idea built or added onto previous usage or practice [6].

Surgical innovation

In surgery, innovation is often a stepwise adjustment in everyday practice when existing and well-established procedures are constantly adapted to the personal needs and requirements of each specific patient condition, or to surgical experience. Therefore, it is rare for completely novel techniques to be introduced "out of the blue" into daily practice in one stage. There is hardly any field of surgery where technical improvements are pushed forward so forcefully as in the field of endoscopic surgery. This progressive modification of established practice may even appear initially as an undesirable change within the attempt to address a problem or clinical condition and may only later and retrospectively prove to be an advance. Margo states that "innovation through deviation from standard practice is an important means of improving surgical care and needs to be encouraged even if results may not always turn out as expected" [7].

In the following section, the distinction between innovation and modification as well as "me-too" technology will be clarified, as this distinction is essential for the practice of a new health technology in surgery.

Distinction between innovation and modification/"me-too" technology

For our purposes, the term "new health technology" covers new or modified surgical procedures, new or modified medical devices for use in surgery as well as "me-too" technologies (Tables 1 and 2). New technologies range from minor changes of an established surgical procedure to the development of new implants for a novel surgical technique [2]. New surgical procedures, for example, often evolve in small steps. Generally, it is not easy to decide when a new health technology is innovative and should be subjected to formal review [8].

Thus, before the process of the preclinical and clinical scientific development of an innovation starts, it is necessity to decide whether a new health technology can be regarded as an "innovation" (Fig. 2, Box 1).

A surgical innovation implies significant differences from existing practice [9] in terms of medical and/or economical outcomes (Table 1). "Significant differences" to existing practice can only be judged for the specific technology; they should be apparent in certain situations [7]. They should be assumed if—based on preliminary knowledge—relevant advantages or disadvantages in key outcomes can be anticipated. However, a grey zone exists regarding the term "significant" [10]. If the outcome in terms of benefit and risk is unknown, the term "innovation" would apply to a novel therapy that *eventually* is shown to be effective and is something that the public needs or wants [11]. In this case, the innovation is initially a "potential innovation" or "promising technology" with an *expected* or *anticipated* additional benefit, whose additional benefit compared with the standard technology has not yet been evaluated.

If the innovation is a novel therapy that is already fully evaluated and shown to be effective but not implemented in the certain area it can be denoted as a "real" innovation.

For the following process of the scientific development of an innovation we assume that there is uncertainty about the innovation's outcomes. Therefore, a useful definition of innovative surgery for our purposes is "a novel procedure, a significant modification of a standard technique, a new application of or new indication for an established technique or an alternative combination of an established technique with another therapeutic modality that was developed and tested for the first time" [12].

In contrast to innovations, modifications (or variations) are only minimal changes in standard practice which do not expectedly increase patients' risks and are likely to have a similar outcome compared with standard practice, for

Table 1 Distinction between innovation, modification, and "me-too" technology

	Difference from existing practice	Anticipated outcome	Result of outcome evaluation[a]	Implementation to medical care
"Me-too" technology	No	=	=or unknown	Yes/no
Technical modification (or variation)	Partly	=	=or unknown	Yes/no
"Potential" innovation (promising technology)	Yes	+	Unknown	No
(Real) innovation	Yes	n/a	+	No
Standard technology	n/a	n/a	n/a	Yes

n/a, not applicable

[a] Includes assessment of medical benefits, medical risks, and economics

"+" indicates better than standard practice; "=" indicates similar to standard practice

Table 2 Examples of innovation, modification, and "me-too" technology differentiated by procedure, device, and drug

	Procedure (e.g., appendectomy)	Device (e.g., grasper, trocar)	Drug (e.g., antibiotic)
"Potential" innovation	NOTES	Instruments for single-port surgery	Development of new substance or use of existing substance for new indication
Technical modification (or variation)	Change in trocar placement sites	Screw-like trocar	Application route; retard preparation
"Me-too" technology	Minimal reduction in wound size	Minimal changes in material, design, etc. (unlikely to result in clinical differences); different length of trocar	Minor changes in pharmacologic characteristics

NOTES, Natural orifice transluminal endoscopic surgery

example, small changes in the length or site of an incision to improve access in an operation [13]. However, they may still require some oversight/monitoring [14]. Similarly, "me-too" technologies do not meet the criteria characterizing an innovation. There are no differences from existing practice, and the patient's outcome is similar. They do not require more than actual existing monitoring of this specific technology. An example of a "me-too" technology is a new surgical instrument which varies only in terms of the material.

Examples for innovation, modification, and "me-too" technology differentiated by surgical procedure, medical device, and drug are presented in Table 2. However, the differentiation between modification and "me-too" technology is not always easy, and the boundaries can be blurred.

The benefit of an innovation in medicine may be relative, depending only on the point of view of a limited number of players (patient, physician, industry, health insurance, society) in the health care system. Thus, some forms of innovations can lead to diverse benefit, such as cost reduction or simplification of a procedure. *The primary focus of this consensus statement is patient outcome and his or her personal perspective.*

Innovations as defined above have to be subjects of research and should run through preclinical and clinical scientific development.

The essentials of formal research are a scientific hypothesis and the systematic collection of data to prove or disprove the hypothesis [7]. Before initiation of a preclinical or clinical evaluation, the existing evidence regarding the particular innovation has to be systematically searched and reviewed (Fig. 2, Box 2).

Preclinical scientific development

When a novel health technology departs substantially from the standard of care and is defined as innovation according to the criteria outlined above, scientific evaluation is required during the development of the innovation.

Scientific development involves generating knowledge and skills according to critical appraisal of existing evidence, conducting preclinical and clinical evaluation, and if needed re-evaluation of the particular innovation (due to improvements and modifications within the evaluation). There is some analogy to pharmaceutical research (phase 1 to phase 4 studies); however, some specifics for health technologies in surgery exist.

Research on surgical innovations has two main objectives:

1. Determination of feasibility, safety, and efficacy.
2. Development of training methods for safe use of the technology by end users.

Related to the second objective, it is important to stress that the users of any new health technology in surgery will include not just the patient and the surgeon but a number of different individuals, clinical and nonclinical, e.g., nurses, technicians, and in the case of reusable equipment central sterile servicing personal (responsible for cleaning and sterilization, etc.)

Testing for feasibility, safety, and efficacy is conducted in two phases as mentioned above: an initial preclinical evaluation, followed by clinical studies (clinical evaluation).

The preclinical evaluation includes testing in simulators of human anatomy and human tissue as well as evaluation on living animals. For simulation, it is necessary, to use as model animal organs and organs blocks with the greatest similarity to the human organ, integrated into a human anatomical surrounding. For evaluation on living animals, both acute (animal sacrificed at the end of the procedure) and chronic (survival) experiments in large animals are essential and have to be performed by an approved research institution for recognition by regulatory bodies. Preclinical animal studies (acute and chronic) require formal approval at the institutional level and, in some countries, e.g., the UK, a special license is required specifically by a national body (the Home Office Inspectorate) for permission to conduct animal experiments. However, there may be some disadvantages of testing on living animals: closeness to human anatomy is not always possible, and the necessity of replicate experiments can make these studies unpractical because of organizational and cost factors.

For the assessment of *clinical* feasibility, safety, and efficacy of surgical procedures or devices, clinical studies are indispensable (see "Clinical scientific development" section).

Problems regarding research in surgery arise due to unstable conditions, especially in the initial phase of an innovation. At the beginning, factors which impact on outcome include the proficiency-gain curve, as distinct from the learning curve [15], of the surgeon in performing the intervention to a predefined standard, and any modification of the surgical procedure. Differentiation between proficiency-gain and learning curves is important, especially in the context of the execution of new procedures, and is addressed later in the document.

Feasibility and preclinical safety must be established before innovations become subjects of clinical research (GoR A, 100%).

The preclinical feasibility and safety of an innovation have to be assessed by critical appraisal of existing preclinical data and/or by conducting a preclinical evaluation (Fig. 2, Boxes 3 and 4).

The GoR A level of this recommendation is based on legal requirements. Existence of evidence for preclinical feasibility and safety is a prerequisite for initiating the phase of clinical scientific development. Lack of any alternatives may be an exception and can lead to direct clinical assessment without preclinical evaluation.

If preclinical feasibility and safety are established (according to defined criteria for risk–benefit assessment), approval for clinical research can be given by an external institution within the constraints of the legal framework pertaining to the particular country (Research Ethics Committee).

Clinical scientific development

The clinical feasibility, safety, and efficacy of innovations must be established before they are widely used on patients (GoR A, 100%).

The clinical feasibility, safety, and efficacy of an innovation have to be assessed by critical appraisal of existing clinical data and/or conducting a clinical evaluation (Fig. 2, Boxes 5 and 6). The prerequisite for wide use of the innovation on patients, i.e., use in routine care beyond clinical research, is the existence of evidence for the clinical feasibility, safety, and efficacy and the corresponding scientific approval.

The critical appraisal of existing evidence should be geared to the methodical quality of evidence [level of evidence according to the requirements of evidence-based medicine (EBM)]. Ideally, only studies whose design and performance minimize bias should be included in the formal assessment. However, the selection should depend on the suitability of the evidence for the intervention under consideration [13]. This includes the assessment of the internal and external validity of research by asking: (1) Are the conclusions trustworthy (internal validity), and (2) how does the research apply to one's own daily practice (external validity)? [16]. Furthermore, issues of previous training and previous volume of experience of operators should be considered within the critical appraisal of the evidence [17]. The extent of evidence on safety outcomes needed depends, among others, on the condition which has to be treated and on the existence of alternatives. Similar to the previous recommendation regarding preclinical development, lack of any alternatives presents an exception to the need for clinical scientific development; that is, an innovation without any alternative treatment might be adopted in routine care without assessment through this phase.

All research involving human individuals or their identifiable data must be reviewed by the appropriate body for ethical approval according to the relevant legal requirements (GoR A, 100%).

This statement applies to all types and each phase of research involving human individuals or their identifiable data, not only for innovations. However, it seems important to state it in this guideline, given that research on surgical innovations (especially novel surgical procedures) is less well established and less formalized than research of drugs and pharmaceutical innovations.

The Commission of the Belmont Report states that "research is usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective" [9]. However, the clinical development of a surgical innovation is determined in many cases by a process of trial and error [10]. Also, innovative surgical procedures that have been developed in animal models cannot simply be transferred from the laboratory to clinical trials in human subjects without further refinements and modifications [7]. Although preliminary testing in surgery may not be standardized as for phase 1 and phase 2 drug studies, these initial phases are to be considered as part of a research project and should be reviewed by an appropriate body for ethical approval. The appropriateness of the body for ethical approval depends on the legal requirements in each particular country.

Within the development of an innovation a distinction between "innovators" (=inventors) and those who only implement an innovation in other centers ("early adopters") seems to be useful.

If there is insufficient clinical evidence to prove safety and efficacy, clinical evaluation must be initiated in

order to achieve the appropriate level of evidence (which does not necessarily have to be a randomized controlled trial) (GoR A, 100%).

When initiating a clinical evaluation several factors have to be considered, such as the learning and proficiency-gain curve, identification of confounders to minimize systematic bias, training requirements, and demands of the investigator (study center), which are addressed later in the document. The appropriate evaluation depends mainly on the nature and the complexity of the innovation. The complexity of a surgical intervention is affected by factors such as the surgeon and other members of the team (e.g., anesthetists, nurses, technicians) as well as the perioperative management [18].

The initial clinical experience must be prospectively documented and continuously evaluated according to prespecified criteria covering clinical feasibility, safety, and efficacy (GoR A, 100%).
The results of the initial clinical experience must be submitted to the responsible ethical body (GoR A, 100%).

Initial patient application

The clinical introduction of a new health technology is one of the most crucial steps in the pathway of innovations in endoscopic surgery. It is during this phase that the initial, innovative idea meets the patient for the first time. Initial clinical application has tremendous implications regarding the expectations of the innovators, the responsibility of the therapists and the involved organizations such as the hospital and the health insurance of the patient, and last, but not least and most importantly, patient safety. Prior to clinical introduction all necessary prerequisites must have been fulfilled, such as the technical feasibility of a given new diagnostic or therapeutic device and/or new diagnostic or therapeutic procedure in endoscopic surgery. In addition, all necessary regulatory obligations for a new tool and the approval process must have been observed.

The preconditions for use of the new health technology in patients include: (1) rigorous preclinical assessment of the technical functionality and safety of the new device and/or procedure, and (2) training of the surgeons in its proper and safe use. The better these preconditions are fulfilled, the lower the risk of technical failure of the new device during the first in-patient procedure. Moreover, the probability of methodical failure of the procedure in the first patient due to possible inexperience of the surgeon or endoscopist is decreased. These two components underscore the necessity of comprehensive preparation of the device by the engineers and extensive in vitro and in vivo experimental training.

With respect to the selection of the first patient, it is important to ensure that the selected patient can provide, prior to and after the intervention, the necessary information to increase knowledge. It is the responsibility of the investigator's team to document any detail of the protocol in order to gain as much valuable detail as possible from the first cases. In particular, adverse events need to be documented and communicated in order to prevent harm to other patients with similar medical conditions.

Research design

For the given innovation, research must aim for the highest possible level of evidence according to current scientific and methodological standards (GoR A, 100%).

According to the nature and complexity of the innovation, different research designs can be used to evaluate its clinical safety and efficacy.

Clinical studies constitute the best method for the assessment of the safety and efficacy of surgical procedures or devices. The methodical classification and principles according to the requirements of EBM are basically the same as for the assessment of drugs. Within the assessment of an innovation the control of known and unknown influencing variables has to be considered. Therefore clinical studies with a randomized controlled design represent the gold standard in the assessment of drugs as well as for nondrug therapeutic interventions [19]. However, surgical trials sometimes pose specific problems, and randomized controlled trials (RCT) are not always feasible, possible or adequate [20] or—depending on the nature of the innovation—not necessary or even not ethical (for example, because of the existence of "dramatic effects"). Thus, alternative designs such as parallel group nonrandomized studies and controlled interrupted time-series studies may be meaningful [21].

Before initiating a RCT or another controlled trial, uncontrolled trials such as prospective cohort analysis [22] may be appropriate. A prospective cohort study can provide meaningful data (e.g., for the sample-size calculation needed for a subsequent RCT) and should be considered before initiating an RCT. It may reveal the need for modification of the technique or technology and identify unexpected complications [23]. In this respect, even single case studies might be useful [24].

Innovations should be studied for safety and efficacy at the earliest time possible [7]. However, different opinions exist in the literature regarding the timing of a RCT. The most appropriate time for conducting an RCT comparing new with established interventions can be difficult to judge

[25]. If (in case of the existence of a learning or proficiency-gain curve) an RCT is undertaken too early, the technique may not be matured sufficiently and the results of the trial become obsolete; if undertaken too late, the new procedure either becomes established (without RCTs) or is abandoned [24].

Chalmers gave some disadvantages and several advantages for randomization to commence with the first patient [26]. One of the most cited disadvantages is that poor outcomes due to inexperience or the so-called learning period may result in unacceptable complications or death. Surgical techniques, for instance, require some training and experience before the technique can be considered to evaluate a new technology for effectiveness. A second argument is that, without early experience, the right questions to be asked to prove efficacy or effectiveness are not yet fully known. Thus, before conducting a RCT, key endpoints and outcome parameters should be identified [27]. On the other hand, one advantage is that, when randomization takes place at an early stage, when it is not yet known whether the new or the conventional treatment will be superior, the time is ripe before nonrandomized data can upset equipoise or opinions are established making randomization difficult, if not impossible. Enthusiasm for new surgical technology has all too often outstripped evidence, leading to adoption before efficacy has been proved; this may waste resources and harm patients. Also, from an ethical point of view, there are rarely sufficiently clear medical arguments arising directly from patient selection to influence the conduct of the trial. Furthermore, randomization may meet with fewer objections, thus helping to guarantee that reliable data will be gathered from the beginning. Another, very important but usually overlooked reason for randomization from the first patient is that, in real life, all practitioners embarking on a new technology have to go through their learning period; data from this period should be included in the overall evaluation of the innovation, because they give an idea of how easy or difficult it may be to implement or generalize the technology if it is adopted.

Relevant safety and efficacy outcomes

Within the conception of a clinical study is a need for defining patient-relevant endpoints, such as mortality, morbidity, and health-related quality of life [28], providing evidence for the benefit of an innovation in comparison with the standard method. This includes estimating the risk–benefit ratio. Judgements about safety include considerations of the severity and frequency of adverse effects [17]. In decision-making, evidence of outcome measures with direct relevance to patients weigh more than clinical surrogate parameters [17].

Bias and obstacles in surgical studies

Compared with clinical studies on drug interventions, studies in surgery, especially RCTs, are often associated with specific problems [29] and, in particular, structural and cultural obstacles. For example, the feasibility of a clinical trial in surgery can be constrained by surgeons' and patients' preferences for certain treatment options. Similarly, if a treatment is already widespread or accepted as a standard, it becomes very difficult to justify testing it against placebo or even in a controlled trial.

Furthermore there are several technical problems. For example, blinding of surgeons or of patients in RCTs is difficult if not impossible. However, blinding of assessors should be used routinely.

Bias can compromise both external and internal validity [16]. In contrast to chance variability, a bias is a systematic error which undermines a study's ability to reveal the truth. Bias may occur before a trial begins, during the trial execution, or after a trial is completed, or they can be overarching [16]. Some of the more important types and examples of bias are presented in Table 3.

Also the *proficiency-gain curve* of surgeons in performing a new procedure may introduce bias in surgical trials, especially as, in addition to long execution times, technical errors and adverse events are more likely during the proficiency-gain curve. Generally, safety problems decrease with increasing experience. The differences within the training period of surgical procedures in contrast to pharmaceuticals are described by the need of a more personalized training system in the surgical field related to the specific skills of the educated person. This includes cognitive as well as manual skills and cannot therefore be accomplished just by publications (Table 4).

Possible bias due to continuous proficiency-gain curve effects must be considered when performing a surgical trial (GoR A, 100%).

The outcomes for many surgical interventions are influenced by the training, experience, and aptitude of the surgeon [17]. Ramsay and colleagues conclude in this respect that "a change over time in the performance of a technology because of learning complicates evaluation and impedes rigorous evaluation" [32]. The incremental development of surgical procedures and medical devices can lead to the need to restart learning and training.

Proficiency-gain curve versus learning curve for a new surgical procedure

Competent performance of a surgical procedure requires both a cognitive element, i.e., knowledge of the component steps of an operation, and their correct sequence, including

Table 3 Important types of bias in surgical research

Bias	Description	Correction
Attrition bias	Systematic differences between groups in incomplete follow-up examinations due to withdrawals exist [30]	Complete follow-up examinations of all patients
Detection bias	Systematic differences between groups in how outcomes are determined exist [30]	Blinding
Differential expertise bias	Systematic differences between groups due to differences in the surgical expertise within the performance of the therapy [31]	Training of study physicians; definition of minimum of operations
Performance bias	Systematic differences between groups in the care provided or in exposure to factors other than interventions of interest [30]	Blinding
Publication bias	Studies that support a hypothesis are published rather than studies which do not	Registry of studies
Referral bias	Differences between the patient population of a study center and the normal patient population lead to restricted external validity of a clinical trial	Multicenter trial design
Selection bias	Systematic differences between baseline characteristics of the groups that are compared exist [30]	Randomization

Table 4 Main differences between medical devices and pharmaceutical products

Medical devices	Pharmaceuticals
Designed to perform certain functions based on quality, safety, and efficacy	Development by trial and selection on the basis of quality, safety, and efficacy
Generally active by physical means	Based on pharmacology and chemistry, now encompassing biotechnology and genetic engineering
Continuous innovation and iterative improvements based on new science, technology, and available materials	Biologically active: effective when absorbed into the human body
Short product lifecycle and investment recovery period	Extensive product lifecycle and investment recovery period
High cost of distribution; intensive user training and education; provision of service and maintenance for high-technology devices	Low distribution costs in most cases; no service; no maintenance
Often integral to clinical procedure, so user training and education are essential for safe and effective use	Training required for use is much less intensive than for high-technology devices

Source: Adapted from Eucomed, Industry Profile 2003

familiarization with all the equipment and devices to be used in the procedure; this is the cognitive or learning curve (LC), and its importance is obvious. In contrast, the proficiency-gain curve (P-GC) outlines the performance of the surgeon in reaching the proficiency plateau when the surgeon is able to perform the procedure consistently well with reproducible clinical outcomes [15] based on predefined quality indicators. In the course of the proficiency-gain curve, the surgeon passes from the controlled conscious mode, which requires attention control, translates into slow deliberate execution, and is subject to fatigue, to the automatic unconscious processing mode, which is effortless, intuitive, fast, and not mentally exhausting. As humans are not machines (never producing exactly the same result), proficiency is described by a zone (Fig. 1) with a lower limit below which performance is unacceptable as defined by the profession and society in terms of clinical outcome and morbidity [15].

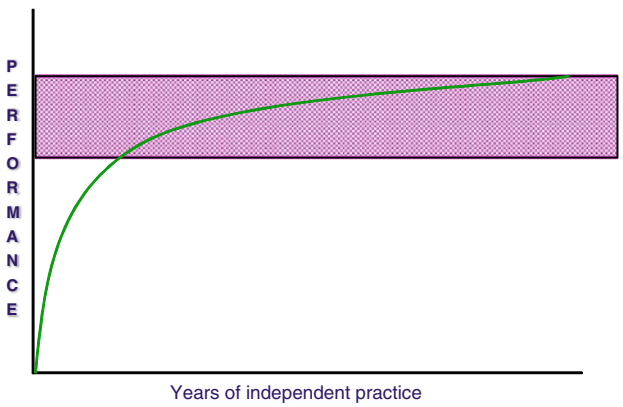

Fig. 1 Proficiency-gain curve

Regrettably, in the surgical literature, the LC and the P-GC are usually, if not universally, used interchangeably. The technique for studying the P-GC for surgical

operations is derived from industrial human reliability assessment (HRA) [33], but whereas this performs a predictive analysis of what may go wrong and its estimated incidence, observational clinical HRA is based on observational data capture (using unedited complete videotapes of the operations) followed by analysis by human factors engineers, and hence it is referred to as observational clinical HRA (OC-HRA) [34–36]. Obviously each new procedure has its own P-GC, requiring a certain number of cases until the surgeon reaches the proficiency zone. Retrospective series are unreliable in providing valid information on the P-GC of new procedures [33].

Proficiency-gain curve effects should be validated in each clinical trial to assure that the outcome is not biased by these effects. Quality indicators have to be defined to monitor the proficiency-gain curve.

Who should do the clinical research?

Certain criteria must be met when the innovation is introduced into clinical practice:

- **Extensive preclinical and/or clinical experience of the innovation involved**
- **Extensive knowledge on the involved diseases and all alternative techniques**
- **A detailed protocol for the procedure and detailed documentation of all parameters prior to, during, and after the procedure**
- **Existence of structural and organizational prerequisites for research (GoR A, 100%)**.

Every surgeon who fulfils the above-mentioned criteria can be called upon to evaluate a surgical innovation. Adopters should be encouraged to gather experience and reach the standard set by the innovator. A further condition for clinical research is the confirmation that an ethics committee has approved the possibility of performing the new procedure for the first time in patients of the hospital/clinic. The hospital/clinic should have structural and organizational prerequisites to generate information to increase the knowledge on the particular innovation, e.g., the possibility to conduct follow-up examinations of the patients, if necessary over a longer period.

Training requirements

All those who participate in clinical trials must have attended adequate training (GoR A, 100%).
If the innovation is a new procedure, training must include both preclinical models and clinical experience (GoR A, 100%).
If the innovation is a new device, training should include both preclinical models and clinical experience (GoR B, 100%).
Preclinical models should mimic the clinical situation as closely as possible (GoR B, 100%).
In the starting phase, those who have performed the innovation process must share their expertise with others and participate in training concepts (GoR A, 100%).

Everybody in the team involved in the application of the new technology has to go through a learning and proficiency-gain curve. For participation in clinical trials it should be ensured as far as possible that all operators are nearly at the same level of experience. The individual learning and proficiency-gain curve of the innovator already gives a certain guideline in how to organize the training course and how often it is necessary to repeat the operations. Furthermore, the issue of standardization has to be addressed [37].

Training should include both preclinical models and clinical experience, although learning in models should be a prerequisite for application on patients. The clinical situation should be mimicked in models; that is, they should contain all the components of the clinical procedure which determine the clinical outcome (content validity), though they may not necessarily look identical in a simulator (face validity).

Sharing expertise with other colleagues may be so time consuming that further work on the innovation becomes impossible. However, knowledge acquisition also involves consulting and using videos, publications or any other means of communication. Sharing knowledge also includes reporting of complications, obstacles as well as helping to develop training concepts, and not only teaching in the operating room.

Scientific approval of innovations

A very important step during the development of an innovation is the scientific approval of the innovation (Fig. 3, Box 7). As described in the algorithm this step determines whether and how the clinical adoption of a health-related technology should or could be recommended. Besides necessary legal requirements, the scientific assessment should contain a risk–benefit analysis with necessary clinical evaluations. It should also propose scientific strategies for the bridging of existing knowledge gaps and the development of effectiveness and vigilance data. Based on the nature of the innovation, scientific methods can be adapted and implemented during the adoption phase of an innovation.

The development of an innovation should be finalized by a systematic scientific report summarizing the currently available evidence (GoR B, 100%).

The scientific report may be a HTA report, a qualitative/quantitative systematic review or a clinical guideline.

Existing framework for the admission of health technologies to the market in the EU

Whereas pharmaceuticals have to prove their final clinical benefit during the regulatory approval process and subsequently are reimbursed soon after being licensed, medical devices follow a different regulatory approach, offering easier access to the health care market but a more complicated way of getting reimbursed. Surgical procedures do not have any kind of regulation by law, despite generic health-related legal issues. Incremental developments depending, e.g., on rapid implementation of new engineering knowledge can affect the assessment of the efficiency and effectiveness of a technology. HTA reports have to be open for ease of updating as new reliable information on patient outcomes becomes available.

The process of admission to the market of medical devices depends on the application of the Conformité Européene (CE) label according to European Union (EU) guidelines. The CE label of medical devices attests to basic requirements such as quality, safety, harmlessness, and achievement of purpose. In contrast to drugs, medical devices do not interact with a patient directly but through an intermediary (the health care professional) [38]. The European Medical Devices Directive (93/42/EEC) provides an extensive definition of what a medical device is; however, paramount to this definition is that a device "does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means" [39]. This leaves a very broad and heterogeneous group of products under the headline "medical device," ranging from aids for the disabled including implants, orthopedic devices, dental devices, electromedical and imaging equipment, surgical instruments, to in vitro diagnostics.

For medical devices there is a classification which describes the four risk categories that exist (I, IIa, IIb, and III) [39]. The classification is based on the vulnerability of the human body (invasiveness), the potential risks associated with the possible or actual dispensing, sampling or substitution of energy or substances, and the duration of application. Products with low risk of application and low grade of vulnerability are in class I, such as dressing material and some surgical instruments (depending on duration of application). In class II, risk of application and grade of vulnerability are increased. Examples include several surgical instruments. Medical devices with the highest risk potential (class III) are exemplified by intracardiac catheters and absorbable surgical sutures. As of today, a classification of risk for surgical procedures is lacking.

Potential hurdles for transfer of innovations

In Germany, a study was conducted by the Federal Ministry of Education and Research in 2008 with the aim of identifying hurdles to innovations in medical technology (medical devices as well as operative and other interventional procedures) [40]. Thereby, possible hurdles for transfer of innovations into the market and thus into clinical practice were analyzed by consulting experts who identified possible hurdles, particularly in two phases of the innovation process. Firstly, there is the phase of clinical research and validation, which is associated with high costs; furthermore, there may be a lack of study centers with the necessary clinical expertise. Secondly, accordingly to the opinion of the experts, a barrier to translation may result from reimbursement by the health insurance system (statutory/national health insurance).

Overall, absence of clinical research and validation of medical products, and thereby unavailable clinical data, constitute hurdles for the transfer of innovations in health care.

The systems for approval of medical devices in several European countries present more similarities than variance [41]. However, the rules for reimbursement by statutory or national health insurance differ from country to country.

Some experts recognize increasing dependence of medicine (surgery) on technology [40]. Therefore, better communication and collaboration between physicians and engineers is needed.

Implementation and monitoring

Within the phase of implementation and monitoring, an innovation has to be assessed and validated for its safety and effectiveness in daily clinical routine as well as for its efficiency (Fig. 3, Box 8). The generated data should be used for a systematic health technology assessment (HTA).

Innovations should be monitored for a defined period of time after their introduction (GoR B, 100%).

Ideally a systematic approach such as a registry fulfilling scientific standards should be used (GoR B, 100%).

The necessity for surveillance of procedures and the period of time for monitoring may depend on risk–benefit assessment as evaluated at the end of the evaluation phase.

There is a legal requirement to report serious adverse events associated with the use of medical devices to

national institutions. There is some analogy to drug development, where periodic safety update reporting (PSUR) is required. However, this reporting is not rigorous and usually incomplete.

Standardization

Once a new procedure is tested in a pilot phase the participants of the project should discuss all steps in order to confirm special advantages of the device or procedure as well as possible mistakes or even probability of harm to the patients in a continuous process. Teams performing these new techniques will gain increasing experience with the new device and/or new technique during the learning and proficiency-gain curves. For this process it is important to focus on the limited experience of one or just a few surgeons in order to expedite their proficiency-gain curve and thus optimize the technique as fast as possible. On the other hand it is also important to involve other surgeons and/or endoscopists in the learning process in order to check the applicability of the new technique with less experienced colleagues in order to evaluate the impact of widespread use and feasibility of training for the method. This must of course be done after an initial phase with greatest care to ensure patient safety.

With increasing experience, operators should critically access their proficiency-gain process in order to develop a time-adapted process of standardization of the procedure. This requires continuous assessment of all parameters during all steps of the procedure to ensure that the standardized procedure can meet all safety and learning requirements without compromising patient safety. This process will require step-by-step evaluation of each stage of the procedure to check if improvements are possible.

Strategies for education and training

Once clinical introduction has been successfully performed for a new device or new technique, and a certain standardization has been established by the initial teams who participated in the launch of the new technique, their protocols and documentations of their learning process will provide valuable insight into the best way to train more therapists in performing the procedure. The more complicated the device or the procedure is, the more it is the responsibility of the industry as well as the surgeons involved in the development and launch to ensure provision of the necessary education and training of all new users of the device and procedure.

This responsibility is on the side of the new user. Training in the new situation or in an experimental environment is advisable or mandatory for complicated procedures. Even proctoring and/or additional education for the new technique in special centers should be required for more complex procedures.

In recent years more and more companies are adopting this practice after launching a new product in order to involve new customers in this important responsibility. This is advisable for all involved parties, especially for patient safety and of course also for their legal back-up. In this context, establishing training courses for these devices or procedures is recommended.

Strategies for monitoring

The EU regulatory system contains, among others, guidance on post-market surveillance and the Medical Devices Vigilance System (see MEDDEV guidance documents; these guidelines relate to questions of application of EC Directives on medical devices and are not legally binding [42]). The vigilance system is aimed at improving the protection of health and safety of patients, users, and others by reducing the likelihood of adverse incidents [43]. Recommendations for the requirements of the Medical Devices Vigilance System are outlined in the MEDDEV guidelines 2.12-1 (2007) [43]. These recommendations apply to manufactures, national competent authorities, the European Commission, notified bodies, users, and others concerned with the continuing safety of medical devices.

Premarket clinical investigations (clinical assessment before implementation) have several limitations. Rare complications or problems which only become apparent after widespread use cannot be detected with certainty. Therefore, an appropriate post-market surveillance system is needed. This may include a number of strategies such as databases/registries and surveillance studies [44]. In the context of developing these kinds of studies or registries, possible emerging risks have to be identified.

Prospective patient registries for new surgical procedures may be the best way to address rare, serious complications [45]. Furthermore, routine data and registries can be used for collecting data on resource use and costs [46], which can be used again for the economic evaluation (assessing cost effectiveness) of an innovation.

A registry for surgical innovations should be established (GoR B, 100%).
Criteria for best-practice methodology should be considered (GoR B, 100%).

The quality of registries and the usefulness of the data can vary widely. Therefore strict criteria have to be considered for developing and assessing a registry. A rough division of criteria can be made between scientific and nonscientific quality criteria. Scientific data can be allocated to the domains "data," "organization," "analysis,"

and—in case of an interventional registry—"intervention." Nonscientific criteria relate to protection of privacy as well as legal and ethical issues.

Assessment of efficiency

There is an increasing tendency to include issues of efficiency in research activities. Many countries in the EU have introduced or are beginning to introduce systems including systematic and structured economic evaluation in the decision-making process [47].

Depending on the recommendations of the scientific approval process it might be necessary to extend scientific and clinical evaluations into the field of health economics and social medicine as well as collecting legal statements for the further clinical adoption process.

According to the algorithm, the last step in the assessment of a surgical innovation is the decision on its efficiency, on the supposition that the innovation is more effective or at least equivalent compared with the alternative intervention (the standard) (Fig. 3, Box 9). For this purpose, a health economic analysis, e.g., a cost-effectiveness analysis, has to be conducted. Depending on the perspective of such an analysis, several cost parameters and data have to be considered.

The "No" case (i.e., innovation is definitely not efficient) in the algorithm describes the situation where the innovation is only equivalent compared with the standard, but costs more. Criteria for the decision that the innovation is efficient are the following:

- The innovation is equivalent or more effective compared with the standard, but costs less;
- The innovation is more effective compared with the standard with equivalent costs;
- The innovation is more effective compared with the standard, but costs more [only if there is the (policy) decision that the outcomes justify the expenses].

Table 5 gives an overview of the cost-effectiveness (efficient) criteria (with equivalence option and the option of lower effectiveness compared with the alternative).

Health technology assessment (HTA)

After information on clinical, economic, ethical, social, and legal aspects has been collected, a health technology assessment (HTA) should be done (GoR B, 100%).

The step of assessment of safety, effectiveness, and efficiency within the implementation and monitoring of the innovation should be finalized by a structured report using the concept of HTA. This implies an assessment taking into account ethical, social, and legal aspects as well as the medical and economic evaluation.

Actually HTA is increasingly being used as a tool to assess and decide on funding and reimbursement for a health technology. The preparation of a HTA report can therefore be helpful for the decision-making process.

In case of an extensive clinical vigilance assessment, e.g., by using structured monitoring systems, HTA can be used to assess all data and to prepare the final clinical adoption process.

The following remarks focus on HTA for medical devices in particular. While the overall framework provided by the HTA approach is robust and broad enough to be applied to medical devices as well, there are certain peculiarities of these technologies that deserve special attention.

The general HTA approach has been developed in the past and is summarized in a number of papers and project results. For more information descriptions can be found on the website of the International Network of Agencies for Health Technology Assessment (INAHTA) (http://www.inahta.org/HTA/).

From a policy context, HTA is mainly applied by healthcare payers in decisions on the appropriate use, coverage or reimbursement of new technologies at different points of time in the medical device lifecycle. As a reflection of the fact that most decision-making in healthcare is about whether a new technology should have access to the market and be funded by society, practical application of HTA focuses mainly on aspects around clinical effectiveness and economic/financial impact. Formal assessment of technologies usually occurs at a national health care system level, although HTA is increasingly

Table 5 Cost-effectiveness spectrum

		Effectiveness		
		−	=	+
Cost	+	Not CE	Not CE	CE (if outcomes justify expense)
	=	Not CE	Equivalent	CE
	−	Not CE or CE (for some patients)	CE	CE

CE cost effective

Source: adapted from [48]

being applied at regional and local levels, for example, within individual hospitals. HTA is also used to help inform best practice through the development of evidence-based guidelines.

The purpose of HTA HTA should be used to provide a rational approach to medicine. This includes the reduction of risk, the increase of safety, efficiency, and effectiveness, and most importantly, the improvement of patient outcome by improving health care services. Health technology assessment should be used to improve the adoption of innovative health technologies by promoting the use of those technologies that are clinically and cost effective. In addition HTA helps to identify out-of-date services and technologies and foster better services and up-to-date technologies. By doing this, HTA is also supporting disinvestment decisions.

From a payer's perspective, HTA is used for informed decisions on the reimbursement, coverage, adoption, and uptake of healthcare technologies. HTA describes the existing knowledge and provides an assessment under transparent conditions. HTA itself is therefore not an additional regulatory hurdle when it describes actual knowledge gaps. The focus of regulatory approval for CE marking (safety, quality, and performance) is very different from the HTA effectiveness assessment and should not be mixed. While the data required for regulatory CE approval are, to some extent, context free, data for HTA are largely context specific [49]; that is, the applicability of the data will depend on local treatment practices, local funding levels, and sociocultural factors.

Timing of HTA HTA can be performed during all steps within a health technology lifecycle after the scientific approval step. Nevertheless the final aim of an HTA report, the assessment under daily routine conditions, is not possible within the early phase of an innovation prior to clinical adoption. Depending on the technology, extended monitoring is necessary to collect structured and systematic data in first clinical adoption scenarios.

Therefore HTA bodies need to balance the demands of regulators to decide on the best available evidence in relation to the innovation with the patient's right of access to the best and most useful procedure to reach the desired outcome.

A discussion between all interested parties supports the identification of the optimal time to undertake HTA, taking into account the need for informed decisions on adoption with the available evidence. This is particularly important when considering devices intended for surgical use, which are often associated with a learning curve effect whereby their effectiveness can only be properly evaluated once healthcare professionals have adjusted their practice to incorporate the new technology.

There are two major differences between surgical procedures and medical devices on the one hand and pharmaceuticals on the other hand which should be taken into account during the assessment process:

1. The way the health technology is being adopted and to what extent training of the health care professional is needed to ensure the patient benefit of the health technology
2. The way the health innovation is being developed and regulated before it is adopted into the health care system

Impact of HTA on innovation With some health technologies the impact of HTA lies in the type and rate of innovation. In those that are characterized by a more constant stream of incremental innovation, there is a danger that, once a rigorous HTA is completed, the next technology generation is already around the corner, leaving the findings of the HTA only applicable for a limited period of time. If HTA introduces significant new challenges to market entry, then there is a potential that this may impact on the rate of innovation.

From the perspective of improving health care services, HTA has two aims:

1. To support the timely implementation of "real" innovations and to describe the environment in which the benefit of the innovation is highest.
2. To avoid the widespread dissemination of unnecessary and/or harmful health technologies.

A negative HTA does not necessarily mean that the innovation is generally harmful or unnecessary, as multiple factors can influence the outcome of an HTA in both directions. Newly available evidence can lead to a different outcome when an HTA is updated. Where knowledge gaps exist, the description of these gaps can even lead to an improvement of the clinical evaluation process. Last but not least, using the HTA methodology can improve the development of knowledge needed to decide on a specific technology.

Ethics

Ethical issues are widely regarded to be an inherent and indispensable dimension of medicine; yet, when it comes to concrete questions, clear concepts and sound arguments may not always be available among those involved. Therefore, the four generally recognized ethical principles are summarized in the following: the respect for autonomy, beneficence, nonmaleficence, and justice [50].

Respect for patient autonomy (informed consent, shared decision-making, substitute decision-making)

For more than 100 years Western societies have made efforts to establish the tradition of enlightenment and civil rights in their medical sectors [51]. This development has been characterized by increasing codification of health care, often responding to violations of values and norms of patient rights, fairness or safety. Serious backlash to progress has been observed not only in totalitarian regimes due to inhumane practices such as Nazi medicine, but also in more recent decades and democracies [52–55] and emphasizes the necessity for awareness and transparency in order to prevent recurrent violations.

Based on the principle of respect for autonomy, individuals have the right to make a *free and informed decision* about participating in a study or about undergoing treatment, particularly invasive measures. Obtaining informed consent for such interventions as a key ethical doctrine has been recognized in international legislation [56]; it is mandatory, and all exceptions to this rule require appropriate reasons, e.g., an emergency situation. Informed consent procedures have to be carried out particularly carefully regarding uncertain or risky interventions, especially when the benefit for the patient is not evident.

With unconscious or cognitively impaired adult patients obtaining informed consent is also necessary, yet it requires an *entitled substitute decision-maker*; this should be realized in advance. Emergency situations may justify exceptions to the rule.

Parents are normally entitled to give informed consent for their children, taking into account that the wishes of the pediatric patient should be acknowledged as well, depending on their developmental maturity. Parents as well as substitute decision-makers have to respect the *patient's best interest*.

Obtaining informed consent requires *communicative skills* and a *respectful attitude*; a successful result can be qualified as achieving a *shared decision-making* between the patient (or the substitute) and the physicians offering the treatment.

Nonmaleficence (risk assessment, prevention, critical incident reporting/medical error management)

No informed-consent procedure, and not even the factual consent of a patient, can justify practicing interventions that damage the patient's health or life without important reasons such as a potential benefit for the patient. The principle of nonmaleficence, thus, is not a procedural but a substantial principle. Therefore, the risks of an innovative intervention need to be described, weighed, and agreed upon in the respected scientific community before offering the treatment to patients:

- Clarify the state of the art and the agreement regarding the acceptability and indication of innovative procedures within the scientific community (databases, guidelines, recommendations, exemplary cases, court decisions, etc.).
- Plan using innovative interventions beforehand and integrate them into your procedure of obtaining informed consent, even if they serve as a second-line option in your plan.
- Be clear about the pros and cons when comparing the specific risk–benefit balance between different treatment options, including your preferred innovative intervention, and integrate your conclusions into your counseling of the patient in an appropriate manner.

Beneficence/ratio between nonmaleficence and beneficence (quality improvement, patient satisfaction)

Like the principle of nonmaleficence, the obligation to help the patient in need and to further his or her well-being is not a procedural but a substantial principle. Thus, the benefit of an innovative intervention needs to be described, weighed, and agreed upon in the respected scientific community before offering the treatment to patients.

The most needed information is the anticipated ratio between the expected benefit and the risks and burdens of an innovative intervention.

Besides the prevailing clinical aspects of benefit that have to be substantiated by evidence-based research, also the subjective qualities of the treatment's benefit are important, especially patient satisfaction with both outcomes and procedures. The communicative qualities of informing and counseling the patient are prevailing, as well as the willingness of health care professionals to respond to the patient's questions, uncertainty or anxiety patiently and even repetitively. Physicians also need competence to address complaints or respond to undesired outcomes or errors and mistakes in a professional and respectful way. However, in the event of a major adverse event in which a particular physician is implicated and which results in a formal complaint, the matter is addressed by an independent complaints committee/inquiry in which the physician does not participate, although he or she has the right to be represented and indeed may be called before the committee/inquiry.

In summary the following aspects should be considered:

- In addition to carefully considering any undesired outcomes of an intervention, focus on the evidence of the benefit that you want to achieve by using the innovative procedure;
- Make your conclusions transparent to the patient in an honest and understandable way;
- Regarding undesired outcomes, medical error or mistakes occurring in the treatment, openly address the

issue and the consequences this may have for the patient—including suggestions for possible help—in a respectful and honest way.

Justice (access to care, equity, fair allocation of resources, problem of implicit rationing at the bedside)

The health care sector throughout Europe has developed a longstanding culture of solidarity and equity that has received appreciation worldwide. Along with the dynamic technological advancements of medicine and the demographic changes in an aging society the general availability of medical care for all may be challenged. Society may split into those who can and those who cannot afford health care or certain interventions; this may even concern measures that are regarded as standard treatment [57]. This results in inequity and injustice, when access to treatment is denied without referring to transparent and fair rules. Not only for traditional reasons, but also in order to protect the high values of human rights and appropriate health care for all, as well as societal peace and trust, arises the obligation that the medical system takes these issues seriously and addresses problems resulting from (possibly covert) rationing or discrimination at the bedside. Too little, i.e., undertreatment, as well as too much treatment ("futility") represent two sides of this coin [58, 59]. Respecting the principle of justice in health care includes actively maintaining an attitude of fairness, especially toward those with greater needs, and using resources carefully in order to avoid unnecessary burdens to patients and society [60].

Further ethical challenges

Protecting vulnerable patient groups/individuals (especially children, but also incompetent patients, prisoners, ethnic minorities, socially marginalized persons, etc.) Multiple studies have revealed specific, often unnoticed, tendencies among health care personnel to put marginalized patients at disadvantage, e.g., by implicit rationing [57, 58]. This may also apply to elderly or female patients, although they are not minorities in the strict sense. Also pediatric patients suffer from particular disadvantages, when they are excluded from innovative treatment on principle because protocols including children seem too demanding or complex to researchers. Finally, patients with rare pathologies ("orphan diseases") suffer from disadvantage due to lack of interest in their condition and treatment [61].

Procedural ethical rules for making hard decisions (such as dealing with conflict of interest, medical error, etc.) The above-mentioned ethical principles have a substantive quality that has potential to orient ethical deliberation, especially in a concrete situation or case. They avoid fundamentalist moral implications and offer considerable latitude for application to concrete issues. However, as opinions often differ, even throughout ethical discourse, also procedural ethics recommendations are necessary.

Ethical recommendations and policies

Orientation for ethical decision-making is given in ethical policies or in specific recommendations that are included in general guidelines (such as this one). This kind of aid can serve as a general indication about which principles, rules, and values need to be taken into account. Some go farther and allow for seeking advice in very concrete questions, especially regarding medical treatment. However, they all require some skills of application and interpretation [51, 62].

In situations of ethical uncertainty or disagreement, which often occur at the bedside [63], an "ethics consultation" should be carried out with the help of a qualified clinical ethics support service. Clinical ethics consultation is a well-developed field with international references (e.g., [64–66]). Where this service is not available, also a more informal discussion of the ethical problem may be helpful. In this case, a moderator who is not involved in the acute problem should chair the session and take care to involve the views of all those affected—in person or by representative—or at least by taking their perspective. The chair, or an assistant, should take well-structured minutes of the meeting to document how ethical issues were taken into consideration and were reasoned carefully. This may be instrumental to prevent legal problems and to contribute to prove good ethical practice retrospectively.

Regulatory ethics paradigm (REP) of innovations

The Belmont Report [9] has been widely used by regulatory authorities such as the Office for Human Research Protections (OHRP) in the USA. The important mandate of the Belmont Report insofar as innovation is concerned reads: "radically new procedures […] should be made the object of formal report at an *early stage* in order to determine whether they are safe and effective." In essence, the Belmont Report takes the view that formal clinical research that aims at establishing the safety and efficacy of new interventions is mandatory and can usually be carried out at an early stage in the development of novel interventions. Thus, it requires that innovative treatment needs evaluation by a formally approved research protocol. The policy of the OHRP is based on the directives of the Belmont Report; as a consequence, the OHRP considers that, without review by a Research Ethics Committee (REC) or equivalent, no innovation can be conducted in an ethically defensible fashion. Furthermore, the OHRP requires the

preparation of investigational protocols according to sound evidence-based methodological standards, implying that innovations that are not validated rigorously and completely are ethically dubious.

This position seems to be consistent, but is not completely in accordance with the revised Declaration of Helsinki, which stipulates "[…] that in the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment they offer hope of saving life, re-establishing health or alleviating suffering" [4]. Therefore, medical ethicists have recently expressed misgivings on the current situation and are urging revision of this very complex issue [67–71].

In formulating the current REP, the OHRP has assumed that a certain degree of standardization of device, technique or protocol exists at the time of the initial introduction of a medical innovation in medical practice. This may not be the case, as not infrequently a significant and complex development process is required for an innovation to mature to the stage where formal research is feasible and meaningful. There are numerous examples of medical innovations which underwent further technical development after their clinical introduction but they all shared the same *clinical background in addressing an unmet clinical need, i.e., no or ineffective therapies.* Some have thus rightly argued that the existing REP does not cope effectively with the complex process of medical innovation. In addition, the typical REC review is conducted by committees whose remit is to judge the scientific merit of the application, which is not always possible in the early phase of a medical innovation. Clinical protocols addressing practical clinical concerns and endpoints rather than scientific hypotheses are needed in the clinical assessment of medical innovations. There are certainly some forms of medical innovations which cannot be regarded as research (driven by a hypothesis with an appropriate protocol to confirm or refute the null hypothesis). Such being the case, the REP based on the Belmont Report and the OHRP policy may not represent the best possible process for the required ethical safeguards in the introduction of innovative care. Bioethicist Agich [67] has come to the view that we need to think beyond Belmont and, in so doing, pay closer attention to the actual clinical, institutional, and professional processes that operate in the development and clinical translation of novel therapeutic innovations—a new set of rules which protect the rights and welfare of the patient undergoing novel interventions while addressing the requirements for practical clinical evaluation as being distinct from scientific protocols for the initial introduction of clinical innovations whose safety and efficacy have been confirmed by preclinical animal studies. This is especially the case when the innovation addresses previously unmet clinical needs; then the innovation would be in line with the revised Declaration of Helsinki.

Directives

The following ethical directives arise from the explanations given above.

1. The patient (or surrogate decision-maker) must be informed of the innovative nature of the procedure before the intervention, even if it is a common practice in other parts of the world already.
2. The process of obtaining informed consent must include a discussion of alternative treatment options.
3. A complete description of the critical elements of the proposed procedure, the expected outcome(s) and benefit(s) of the procedure, and the foreseeable risks must be included in informing the patient.
4. The responsible physician must make sure that the patient understands the information, has appropriate opportunity to get his or her questions answered, and has enough time to think it over before deciding.
5. The possibility that innovative procedures are being applied without previous planning during the operation must be addressed in the standard informed consent procedure.
6. The patient must have the chance to refuse the suggested options.
7. In the case of an unanticipated application of the innovative procedure during the operation, this must be disclosed postoperatively.
8. If a device is used "off-label," the physician must determine the relative risk and disclose it to the patient as part of the informed consent process.

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Appendix

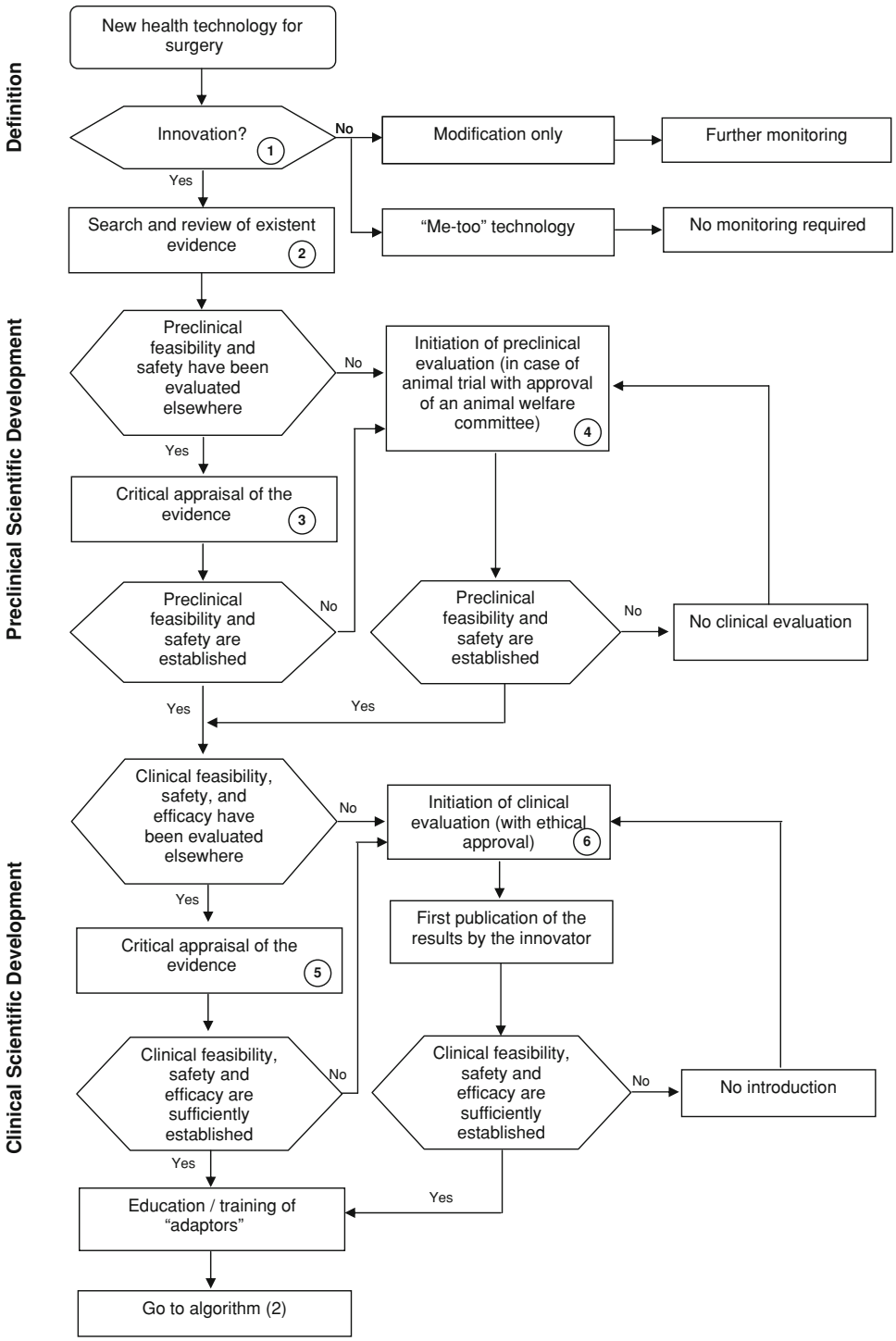

Fig. 2 Algorithm 1 for the definition and scientific development of innovations for surgery

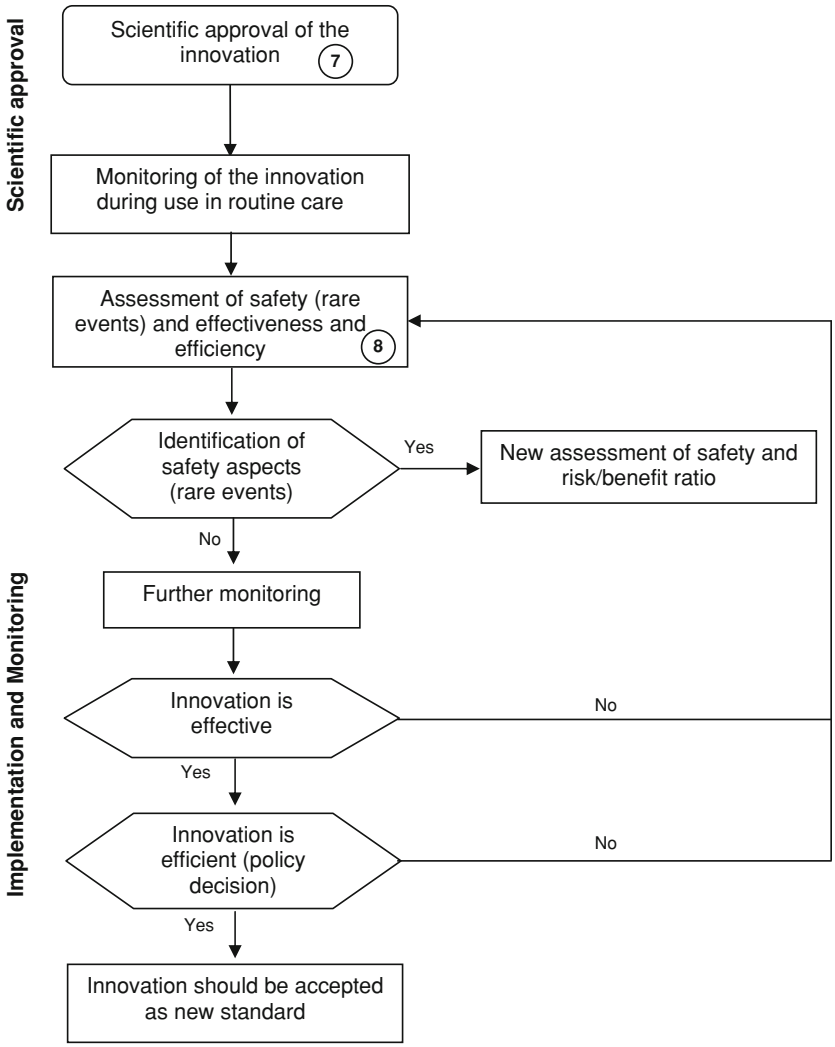

Fig. 3 Algorithm 2 for the scientific approval and implementation and monitoring of innovations for surgery

Glossary

Appraisal of evidence: formal assessment of the quality of research evidence and its relevance to the clinical question or guideline under consideration, according to predetermined criteria [72].

Critical appraisal: the process of assessing and interpreting evidence by systematically considering its validity, results, and relevance [73].

Efficacy: the extent to which a specific treatment or intervention, under ideally controlled conditions (e.g., in a laboratory), has a beneficial effect on the course or outcome of disease compared with no treatment or other routine care [72].

Efficiency: the extent to which the maximum possible benefit is achieved out of available resources [73].

Effectiveness: the extent to which a specific treatment or intervention, when used under usual or everyday conditions, has a beneficial effect on the course or outcome of disease compared with no treatment or other routine care. (Clinical trials that assess effectiveness are sometimes called management trials.) Clinical "effectiveness" is not the same as efficacy [72].

Ethical approval: an independent review of the scientific merit and implications of a study regarding the dignity, rights, safety, and well-being of research participants [74]. All primary research on humans has to be first approved by a Research Ethics Committee (REC).

Evaluation: assessment of whether an intervention (for example, a treatment, service, project or program) achieves its aims. The results of evaluations can help in decision-making and in planning future policies. Process evaluation is an ongoing examination of the intervention from its conception to its delivery and includes staff performance, methods, activities, effectiveness, and efficiency. Outcome evaluation is an assessment of the immediate or midterm effects of an intervention or some aspect of an intervention [72].

Feasibility (technical): the process of proving that the concept is technically possible.

Health technology assessment: systematic evaluation of properties, effects, and/or impacts of health care technology. HTA may address the direct, intended consequences of technologies as well as their indirect, unintended consequences. HTA is conducted by interdisciplinary groups using explicit analytical frameworks drawing from a variety of methods [73].

Identifiable data: information that allows the identification of the survey respondent or data provider that it relates to its identification to be determined either directly (e.g., by name, address, reference number) or indirectly (e.g., by some distinguishing feature such as business activity, size, location) [75].

Research Ethics Committee (REC): committee that has the task of evaluating research proposals for approval, and also gives advice for the improvement of research protocols. In their work RECs rely on international guidelines such as the Declaration of Helsinki [4]. Some health care institutions have Clinical Ethics Committees that may be the appropriate body for ethical advice and approval. Also, the national medical associations have Research Ethics Committees that, depending on the respective legal requirements, may have to be approached for ethical approval.

Safety: judgment of the acceptability of risk (a measure of the probability of an adverse outcome and its severity) associated with using a technology in a given situation, e.g., for a patient with a particular health problem, by a clinician with certain training, or in a specified treatment setting [73].

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