Towards early and broad evaluation of innovative surgical devices: integrating evidence synthesis, stakeholder involvement, and health economic modeling into the clinical research stages of the IDEAL framework

Mirre Scholte, Kas Woudstra, Janneke P C Grutters, Gerjon Hannink, Marcia Tummers, Rob P B Reuzel, Maroeska M Rovers

INTRODUCTION

New surgical devices are entering healthcare systems at an unprecedented pace. Scientific evaluation of such devices is, however, perceived to lag behind that of new drugs. Although innovation is often seen as a positive development, it is currently hard to predict or establish how innovative devices improve surgical care.

While new drugs must show substantial evidence of effectiveness and safety through clinical trials, medical device regulations in the European Union and the United States of America have historically focused on proof of safety as a minimum requirement. In recent years, both regulations have been updated and now demand clinical effectiveness for high-risk devices, but still allow some surgical devices to gain market approval with little or no clinical evidence. To improve the quality of research for surgical devices, the IDEAL collaboration has adapted their five-stage evaluation framework (Idea, Development, Exploration, Assessment, and Long-term follow-up) to specifically provide recommendations for clinical studies on innovative devices (IDEAL-D). The collaboration aims for evaluation that results in rigorous, safe, and fast evidence gathering, using not only clinical studies but also approaches such as stakeholder consultation, modeling, and cost-effectiveness studies.

The recent attention for these other methodological approaches is important, as clinical trials are expensive and the capacity for conducting these trials is limited. Ideally, only devices that have the greatest potential to improve healthcare and are aligned with the needs and beliefs of involved stakeholders are selected for clinical trials.

This requires methods that enable evaluation of surgical devices from a very early phase and allow for an evaluation that is broader than the analysis of clinical effects. Developing and applying such methods has proved to be difficult, as the earliest stages of innovation are characterized by large uncertainty and a lack of evidence. In these situations, it is tempting to delay solid evaluation or to only include direct, tangible, effects. The potential risk is that devices are developed that are not desirable, effective, affordable, or supported by stakeholders. To avoid this risk, methodological approaches are needed that allow for an early and broad assessment. However, little is known about which methodological approaches can be used and how these methodological approaches should be integrated in the IDEAL framework. In this paper, we therefore take a first step towards an iterative approach and show how evidence synthesis, stakeholder involvement, and health economic modeling can be integrated in the IDEAL framework. To make this more tangible, we describe an empirical case study demonstrating our approach in clinical practice. It contains an example of one of our previous projects and the lessons we have learned during this project.
INTEGRATING EVIDENCE SYNTHESIS, STAKEHOLDER INVOLVEMENT, AND HEALTH ECONOMIC MODELING INTO THE CLINICAL RESEARCH STAGES OF THE IDEAL FRAMEWORK

Element 1: evidence synthesis

Evidence synthesis refers to the process of bringing together information from a range of sources and disciplines to determine what is already known, and is ideally the first step in our approach. It is important to look at current clinical practice, the innovation, and the healthcare system. Hereby, information on the performance of current practice and the healthcare system can be generated, as well as information on innovation characteristics and the existence of other innovative, competing techniques. This provides a solid evidence base for further research and development (R&D) and can avoid developing devices for indications where other innovative technologies are already being developed. Scientific and gray literature are key sources of information. Appraising the quality of the evidence is a crucial part of evidence synthesis, as low-quality studies could misinform further studies or create diverging opinions among stakeholders.14–16 In our empirical example presented in online supplemental materials, we show how our approach was used in the evaluation of sentinel lymph node biopsy for the management of oral cavity squamous cell carcinoma. The evaluation process took off with an evidence synthesis of international guidelines.

Element 2: stakeholder involvement

Stakeholders should be involved in the innovation and evaluation process. It is important to identify a broad range of stakeholders, because novel surgical devices work most optimally when they are valuable for all stakeholders like patients, relatives, and medical professionals.17 18 We employ qualitative methods for stakeholder involvement, for example interviews, because these methods are most suitable to perform an open and detailed analysis of the problems, solutions, knowledge and values that the included stakeholders describe. It is important to acknowledge that stakeholder might consider different domains in characterizing the value of a device and attach different weights to those domains. During the early evaluation, the interests of different stakeholder need to be brought together in the decision-making process. Interaction between stakeholders to carefully balance these interests is therefore crucial to our approach. Stakeholder involvement will contribute to a broad set of criteria that must be fulfilled for the innovation to have added value and important study parameters or outcome measures to be taken into account in next study phases. In our empirical example, interviews were used to determine improvements in oral cavity squamous cell carcinoma care and highlighted different opinions about the safety and effectiveness of innovative sentinel lymph node biopsy.

Element 3: health economic modeling

Health economic modeling is a relatively quick and inexpensive way of exploring the potential consequences of an innovation.19–22 In our approach, we look beyond the traditional use of modeling, because we believe that early-stage models should not be used as a tool for a definitive assessment of an innovation, but have an exploratory function.18 23–26 The first stages of innovation are often characterized by large uncertainty (eg, about innovation effectiveness; how, when and where to implement the innovation in the care pathway). In this stage, exploratory modeling approaches can be used to explore effectiveness gaps in the current clinical pathway. Next, conditions under which an innovation can be of added value can be explored. It should be used to determine what is needed for all relevant perspectives, such as society as a whole (eg, “could this device bring added value at an affordable cost for society”), instead of only adopting a business perspective (eg, “could this device be commercially viable”). Exploratory modeling allows for multiple scenarios or stakeholder views to be modeled and can deal with the complexity and uncertainty associated with innovation. In this way, health economic models can be used to inform study design, as they identify important knowledge gaps in current practice, determine which parameters should be studied, and set out conditions under which the innovation has added value for society.22 23 25–27 In the empirical example, modeling was used to evaluate the cost-effectiveness of multiple innovative strategies and to explore important uncertainties.28 In a next step, the model was adapted to include individual patient characteristics. In this way, the best treatment option for individual patients could be investigated.29

Element 4: clinical research

To establish the actual added value of an innovation in practice and gain regulatory approval, reimbursement, and adoption in clinical practice, clinical research is needed. By using frameworks such as IDEAL and IDEAL-D next to regulatory requirements, clinical research using the appropriate methodology can be set up for each clinical research phase. IDEAL recommends a gradual approach, with stage 0 as preclinical research containing a wide variety of approaches, including the above-mentioned elements, cadaver studies, usability testing, etc. The clinical stages comprise stage 1 as case reports of first-in-human uses of innovations, stage 2a as prospective development studies describing iterative development of the procedure, stage 2b as prospective exploratory studies describing the efficacy of more or less stabilized techniques, stage 3 as randomized controlled trials or equivalent alternatives assessing the comparative effectiveness of the technique against current practice, and stage 4 as registries to study long-term effects.9–11 Our empirical example shows that not all stages of the IDEAL framework were followed. Only recently, sentinel lymph node biopsy in oral cancer was investigated in a randomized controlled trial.30
INTEGRATING THE FOUR ELEMENTS

IDEAL proposes a gradual approach to the clinical evaluation of surgical innovations. Hirst et al already suggest the use of evidence synthesis, stakeholder involvement, and health economic modeling in IDEAL 0. The novelty and cornerstone of our approach is that these elements should inform each other and that they should be interwoven in each of the stages of the IDEAL framework, as is displayed in figure 1.

For example, evidence can be used to provide an overview of current clinical practice and the healthcare system, and generate a first overview of the innovation characteristics and potential competing techniques. This information can subsequently be used for stakeholder deliberations to determine where in the system the innovation should be placed and what study outcome measures are relevant. These outcome measures can subsequently be incorporated in health economic models. Health economic models explore the room for improvement in current practice, under which circumstances the innovation may provide better outcomes than standard practice and what parameters cause relevant uncertainty and should be studied. All this information can be used to design and conduct a clinical study within the IDEAL framework. Thereafter, findings from these clinical studies form the basis of further evaluation and can be used to update the evidence synthesis, inform stakeholder deliberation, and update health economic models.

We argue that in each innovation process, all elements should be addressed. In this way, a broad scope is ensured which increases the chances of valuable innovation. However, to really steer R&D of new surgical devices towards real added value to patients, healthcare and society, an early starting point, and multiple iterations of the approach are probably necessary, as we have seen in previous attempts of our approach (online supplemental materials). We think that our approach should start as early as possible, with evidence synthesis. Thereafter, elements can be iterated in a non-linear fashion, where unresolved research questions from former elements are used to determine which element or elements are most appropriate for the next phase. This results in an ongoing process throughout the stages of the IDEAL framework where all elements are iterated.

DISCUSSION

Thorough early evaluations can help to optimize innovative surgical devices during the innovation process. We believe that by integrating evidence synthesis, stakeholder involvement, health economic modeling, and clinical research, it is possible to overcome the challenges related to the evaluation of surgical devices. Using this
combination of elements allows to start as early as an unmet need is detected or an innovative idea arises, and take a broad scope during evaluation. This will improve the current evaluation frameworks that are available.

Some remaining methodological issues need to be addressed. First, the suggested approach could initially increase the workload of the already complex innovation process. It is important that the recommended methodologies are accessible and usable by innovators, researchers, and other potential end users. That is why they should closely collaborate, because they hold the experience and knowledge that is needed to make the methods usable and valuable in the innovation pathway.14 In the end, we envision that by using our approach the innovation pathway will be shortened and smoothed, as problems and challenges will be detected in an early phase and can therefore be resolved during the design phase rather than at any later stage when it will be harder to make design changes. Second, the innovation process is often hard to plan in advance, it is probable that the starting point, the number of iterations, and the choice of elements depend on the context and problems of the specific innovation process. At least all elements should be addressed once, but for a thorough evaluation, an early starting point and multiple iterations of the approach are probably necessary. Third, some elements could also benefit from further methodological developments to make them more applicable for innovative surgical devices. For example, there is a need for methods of stakeholder involvement that are feasible and flexible, but still allow for a thorough elicitation of needs and values, as well as health economic modeling methods that address specific challenges related to surgical devices, such as learning curves.

In view of the enormous influx of new surgical devices and their potential consequences, both good and bad, we all have the responsibility to properly evaluate these innovations. In the first stages of the IDEAL framework, methods such as stakeholder involvement and health economic modeling were already mentioned, but no recommendations were made on how to perform and apply these methods.11 12 We have already explored how these methods can be used in the early stages of innovation, and aim to further develop these methodologies so that they can be integrated into the various stages of the IDEAL framework.31 52

By combining the four elements, it is possible to start early and take a broad scope during evaluation. Ultimately, we hope that by using such an iterative approach throughout the innovation process, it will contribute to desirable, effective, and affordable surgical devices.

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SUPPLEMENTARY MATERIALS

Towards early and broad evaluation of innovative surgical devices:
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An empirical example: sentinel lymph node biopsy in the management of oral cavity squamous cell carcinoma

This empirical example aims to demonstrate what the proposed approach looks like in clinical practice. It comprises a description of one of our previous projects about sentinel lymph node biopsy in oral cavity squamous cell carcinoma, which was a novel procedure at that time. Although this case does not present the development of a surgical device, but the innovation of a procedure, we believe the evaluation undertaken in this case can be applied to surgical devices in the same way. Our approach was still under development at that time. That is, the separate steps of our approach – evidence synthesis, qualitative exploration, modelling studies and clinical studies – were followed, but these were mainly considered separate studies, and not integrated as proposed in our approach. Here, we will first briefly introduce the clinical example followed by a description of each step. Then, we will illustrate what our approach has contributed, and what could be improved by integrating the different elements.

The role of sentinel lymph node biopsy in oral cavity squamous cell carcinoma

In 2012, our research group started a project on the role of sentinel lymph node biopsy in the management of oral cavity squamous cell carcinoma. By that time, standard treatment of oral cavity cancer in patients with a clinically negative neck (cN0) consisted of dissection of the tumour with mostly elective neck dissection to treat potential lymph node metastases or sometimes watchful waiting to monitor potential lymph node metastases. Approximately 30% of patients have occult lymph node metastases, which implicated that a large proportion of patients were subjected to a treatment they might not have needed and which is associated with morbidity.[1–4] Watchful waiting, on the other hand, could have resulted in lower survival when occult metastases were present.[5–7] Sentinel lymph node biopsy was a novel and promising treatment approach in which a biopsy is taken from the first lymph node draining a tumour. The procedure provided an intermediate approach between elective neck dissection and watchful waiting, allowing for the selection truly positive patients for further treatment. It could thereby reduce both over- and undertreatment. Nevertheless, strong evidence for the clinical effectiveness or cost-effectiveness of sentinel lymph node biopsy, compared to elective neck dissection or watchful waiting was lacking. It was neither qualitatively explored whether there was a clinical need for sentinel lymph node biopsy, and related wishes and expectations. Our aim therefore was to inform decisions in the management of oral cavity squamous cell carcinoma patients with a clinically negative neck in an evidence-based manner. In the following paragraphs, our findings for each element – evidence synthesis, stakeholder involvement, decision modelling and clinical studies – are described.
Evidence synthesis
A comparison of international guidelines for the treatment of oral cavity squamous cell carcinoma concluded that there was high variation in the management of the neck and that there seemed to be a need to establish more evidence-based management and more uniform practice patterns.\[8\] Also, a diagnostic meta-analysis was performed to systematically assess the accuracy of a sentinel lymph node biopsy in oral cavity squamous cell carcinoma patients with a clinically negative neck. The pooled data showed high sensitivity of 0.93 and suggested a role for sentinel lymph node biopsy in the management of oral cavity cancer.\[9\] This evidence synthesis was performed in line with our recommendations as described in the main text, but could have been applied more broadly to map other innovations.

Stakeholder involvement
The qualitative exploration was aimed at identifying ways in which oral cavity squamous cell carcinoma care could be improved. A pilot interactive evaluation method was used including 9 healthcare professionals and 3 patients. Results showed that participants had diverging opinions about the safety and effectiveness of sentinel lymph node biopsy and whether sentinel lymph node biopsy ought to be used in clinical practice. In hindsight, stakeholder involvement should have been integrated more thoroughly to establish factors that should be taken into account in the cost-effectiveness studies, in or determining the outcome measures for prospective clinical studies. Moreover, policy makers or family members of the patients should also have been included as to involve all relevant stakeholders as suggested in the integrated approach.

Health economic modelling
A health economic model was conducted where five strategies for diagnosing and treating lymph node metastases in N0 patients were evaluated by means of a Markov model.\[10\] The evaluated strategies consisted of existing and novel techniques: elective neck dissection, watchful waiting, gene expression profiling followed by neck dissection or watchful waiting, sentinel lymph node biopsy followed by neck dissection or watchful waiting and gene expression profiling in combination with sentinel lymph node biopsy followed by neck dissection or watchful waiting. The model showed that the sentinel lymph node biopsy followed by neck dissection or watchful waiting was most (cost-)effective. An uncertainty analysis showed that the model was sensitive to changes in assumed incidence of occult metastases and utility values. A second model was created in which individual patient characteristics were included to weigh risks, benefits and costs for individual patients.\[11\] This model showed that a personalized treatment approach resulted in improved health outcomes and cost savings compared to a population approach, but available prediction models should be improved before implementation in clinical practice is possible. Both models meet the requirements of the element as described in our main text, as they help to map the magnitude of the problem, uncertainties and conditions for added value.
Clinical studies
To determine quality of life of oral cavity squamous cell carcinoma patients, a cross-sectional study was set up to inform decision modelling.[12] Furthermore, a prospective clinical study was initiated to measure patient quality of life over time. At the same time several, mostly retrospective, cohort studies about the performance of sentinel lymph node biopsy were published by other research groups.[13–15] In 2020, a large cohort study of 878 patients was published comparing sentinel lymph node biopsy to elective neck dissection.[16] Results showed that sentinel lymph node biopsy is as accurate as elective neck dissection, except for floor of mouth tumours where elective neck dissection seems more accurate. More recently, a randomized clinical trial was published which confirmed that sentinel lymph node biopsy is oncologically equivalent to elective neck dissection, and results in lower morbidity.[17] The results of a prospective longitudinal study regarding the quality of life demonstrated benefit in short-term shoulder function, whereas no significant differences for shoulder morbidity, or health-related quality of life were found at 6 weeks, 6 months, and 12 months between the groups.[18] These results therefore confirm our earlier modelling findings that elective neck dissection is the most (cost-) effective management option. The clinical research phases did not adhere to all stages of the IDEAL framework. We are currently not able to conclude whether a better adherence to these stages would have led to an earlier adoption of the procedure. We do, however, believe that adherence to the IDEAL framework will in the end lead to less research waste.

The merits of an integrated approach
Since the start of this project, standard clinical practice in the Netherlands has slowly shifted towards the use of sentinel lymph node biopsy. It is difficult to determine what exactly has caused this shift, but based on conversations with involved clinicians it seemed that accumulating evidence of the added value of sentinel lymph node biopsy, including the evidence gained through our project, was a major contributor.

All elements of our approach were followed in this case. But in retrospect, we believe that the research into sentinel lymph node biopsy should have started earlier and in a more coordinated way by using the IDEAL framework. The research by individual groups, including ours, could have been better coordinated and integrated. For example, multiple retrospective cohort studies with comparable aims were performed simultaneously. If the different clinical stakeholders involved in these studies would have collaborated, fewer studies would have sufficed. This saves time, money and, perhaps most importantly, lowers the burden of patients. In addition, a staged and more coordinated approach would have allowed to design studies in line with the views of a wider variety of stakeholders, such as patients and relatives. A more integrated research approach would thus have led to a better alignment of the different elements, which can lead to more efficient research practices, and perhaps an accelerated uptake of the innovation.
Reference list


