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Implementing new surgical instruments in minimally invasive surgery

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Citation
Haak, L. van den. (2018, November 15). *Implementing new surgical instruments in minimally invasive surgery*. Retrieved from https://hdl.handle.net/1887/67117

Version:	Not Applicable (or Unknown)
License:	Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden
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Note: To cite this publication please use the final published version (if applicable).

Cover Page

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Author: Haak, L. van den
Title: Implementing new surgical instruments in minimally invasive surgery
Issue Date: 2018-11-15

SECTION A-A
SCALE 1,000

Discussion and Future Perspectives

11

Discussion

Approximately 500.000 types of medical instruments are used in daily clinical practice, ranging from blood pressure meters to advanced surgical robots.[1] Although regulating bodies exist that oversee the introduction of new instruments, a grey area exists whether a new technology is merely an improvement of an already existing and approved instrument or implies such significant changes that would justify generating a new safety protocol. Furthermore, the prudence with which new technology is introduced may often depend on the sense of responsibility of the medical specialist.[2] A growing awareness exists, however, that new instruments inherently have the potential to negatively influence patient safety due to unforeseen side effects. In the past serious short- and long-term adverse events have been described, some of which are discussed in the introduction.[3-7] Several reports were published proposing alternatives to better safeguard patient safety during the implementation of new medical devices.[1,2,5,6] In general, emphasis is placed on proper studies performed in human subjects. As such, randomised controlled trials are considered as highest level of evidence to demonstrate the superiority of an innovation compared to standard techniques. However, we hypothesized that much can be gained regarding patient safety by enhancing the pre-clinical course during the development of a new instrument. In the *leidraad nieuwe interventies in de klinische praktijk* the importance of this course is acknowledged.[2]

In this thesis we focussed on the earliest phase of the development of new surgical instruments, also known as stage 0. It assessed various pre-clinical evaluation methods for new instruments.

Clinically driven approach

Firstly, the concept of a *clinically driven approach* to the development of a new surgical instrument was explored. In general, three approaches exist when trying to enhance daily medical practice. When new technology is devised by the medical industry or by engineers, the approach is called *commercially driven* or *technically driven* respectively.[8,9] Although these approaches can lead to medical devices that are state-of-the-art technically speaking, they may not always meet the demands of clinicians possibly rendering them useless.[9] The *clinically driven approach* starts with identifying a medical or surgical difficulty experienced by the users (i.e. physicians), which is then used as a starting point to create a solution. Usually this implies a close cooperation with technicians and or the medical industry.[10,11]

In our research, the laparoscopic hysterectomy (LH) was chosen as the starting point for exploring the clinically driven approach. The LH is a frequently performed gynaecological

procedure worldwide, but is also considered as technically challenging. Two major topics were addressed.

In **Chapter 2**, we demonstrated that the colpotomy step during LH (meaning the separation of the vagina from the cervix, generally the penultimate step of LH before suturing the vaginal vault) is regarded by gynecologists as difficult and time-consuming. This was substantiated by the measurements of total operation time and colpotomy time. Furthermore, we found that BMI was positively related to colpotomy time, independent from total operation time. As BMI in the general population is rising, colpotomy may increasingly be the limiting step during LH.[12] Subsequently, in cooperation with technicians from the University of Technology in Delft, The Netherlands, an alternative to the current colpotomy procedure was searched. It was proposed that a vaginal approach to colpotomy could possibly overcome present issues with this step in the LH procedure. This resulted in a prototype, called MobiSep, which combines the function of a uterine manipulator and a cutting function to seperate the vagina from the cervix.[13]

A uterine manipulator is an important instrument used during laparoscopic procedures in gynecology as it allows movement and steering of the uterus during surgery. It is proposed that the use of a uterine manipulator should be mandatory because it is said to prevent against ureteric injuries during LH by displacing the ureters from the uterine arteries.[14] In **chapter 3** a literature review was performed as a method to explore the required characteristics that the envisaged prototype should meet. The shortcomings of existing manipulators were used to improve the prototype. It was found that few manipulators offer lateral movement of the uterus, whereas at the same time this movement is regarded as important during ligation of the uterine arteries. Surprisingly, little evidence was found regarding the efficacy of uterine manipulators. For instance, only one observation existed in literature that reported an increase in distance between the ureter and uterine artery due to a uterine manipulator, however methods and materials were not supplied.[15] It is worrying that in the same article it was also observed that the distance can actually decrease due to a mismatch between the size of the cervical cup of the manipulator and the cervix. This would imply that in some cases, there is even more risk of ureteric injuries. Based on the results from our literature review, a study was performed evaluating the relationship between the ureter and uterine artery with and without a manipulator. In one case an increase was observed between the two structures.[16] However, this could not be replicated in the second case. [oral, Lieng] In conclusion, important insights were gained, not only regarding the characteristics of the prototype, but also regarding the workings of uterine manipulators in general.

The next step in our *clinically driven approach* was to assess the prototypes performance and to evaluate if changes should be made before the instrument is ready for a clinical

trial. However, an ideal model in which the new prototype had to be tested could not be found. Animal models are generally not representative due to different anatomy of the internal genitalia. In addition, currently available virtual reality tools bear little resemblance to real life conditions such as tactile feedback. For training purposes, human cadavers have been shown to be a valuable method to improve surgical skills. [17-19] Furthermore, human cadavers were preferred over virtual reality simulators. [20] Based on these findings, in **chapter 4** we decided to assess human cadavers as a model for testing new surgical instruments. Fresh frozen cadavers were chosen as they were favoured in training purposes with respect to tissue appearance and handling. [19,21] The results from the cadaver tests demanded that extensive modifications were applied to the prototype. Although the MobiSep was extensively tested in an in-vitro model, serious anatomical shortcomings of the design were encountered that were not revealed by the in-vitro model. As such, the cadaver tests added essential information to the developmental phase of MobiSep. However, significant limitations were encountered of cadavers as models. Only two of six human cadavers resembled normal anatomy of the internal genitalia. Other cadavers could not be used due to restrictions caused by age-induced atrophy, congenital abnormalities and a malignancy occupying the complete small pelvis. Unfortunately, the medical history of a cadaver is not disclosed due to privacy legislation. Given the low efficiency, it is questionable if human cadavers should be used on a larger scale during the pre-clinical assessment of new technology. In this light, the ongoing developments in 3D printing are of interest. Recent papers have studied the value of 3D printed models for training purposes, and the feasibility of creating representative models of human anatomy has been demonstrated.[22-24]. Several applications already exist in clinical practice. For instance in orthopaedic surgery, 3D printing is already used to preoperatively adept surgical plates and screws to a patient's anatomy.[25] However, currently the main shortcoming of 3D printed models is the lack of resemblance to the natural compliance of human tissue.[26] When this issue is resolved 3D printing will ensure a major improvement of stage 0 of surgical innovation.

The second topic that we addressed concerns power morcellation in laparoscopic hysterectomy and myomectomy. It was observed that during morcellation, small tissue particles are dispersed throughout the abdomen (called tissue spill or spillage). In case of uterine malignancies, it is believed that this tissue spill causes upstaging of the disease and can therefore negatively affect a patient's prognosis.[27,28]

We attempted to address this issue by improving the power morcellation instrument. To this end, we first examined the onset and characteristics of tissue spillage during morcellation in **chapter 5**. Next, in **chapter 6** instrument characteristics that could influence the onset of tissue spillage were assessed. Important inefficiencies were demonstrated of the power morcellator mechanism available at that time. The onset of

torque (also called moment of force) was found to be the cause of tissue spillage. Torque is a rotational force applied to an object. Ideally the rotational blade of a morcellator only slices tissue without applying force to the tissue. However, due to torque, the sliced tissue starts to rotate uncontrollably resulting in tissue particles being dispersed through the abdomen. It was observed that only at the very beginning of the morcellation procedure large tissue segments were created by the instrument. During the majority of the procedure (60%) only small particles were created. These smaller fragments are easily subjected to torque. Also, the amount of tissue spillage was not linearly related to uterine weight, suggesting that after a certain point the risk of tissue spill increases significantly. Finally, it was found that larger diameters of the morcellation instruments (up to 20mm) and an oscillating blade rather than a rotational mechanism all decreased the amount of spill. These findings offered valuable information regarding the shortcomings of the current morcellators that were previously unidentified. Although the devices have been improved through time regarding speed of morcellation, no initiatives were taken to assess other parameters.[29] For our study, beef tongue was used as a model for the human uterus. This cheap and easily obtainable material matches the consistency of the uterus well and was successfully used in other studies.[30-32] Also in our assessments, beef tongue resembled uterine tissue very well. Thus, for simple and straightforward testing of instrument characteristics expensive models are not necessary.

Interestingly, the finding that larger instruments create less tissue spill and may therefore be safer appears to be in contrast to the ongoing developments in minimally invasive surgical techniques. More and more, the invasiveness of surgical procedures is reduced as much as possible as is shown by developments in laparoendoscopic single-site surgery (LESS) and natural orifice transluminal endoscopic surgery (NOTES). However, the benefits of these procedures are not always clear and possible risks have been described. [33] Apparently, smaller is not always better. After identifying torque as the main cause of tissue spillage, it was quickly understood that morcellation instruments with a smaller diameter cause more spill since torque is applied earlier the process.

The findings from chapter 5 and 6 were used to enhance the current morcellation mechanism. In **chapter 7** a prototype is discussed that resolves the problem regarding torque. Inspired by the lamprey, a fish resembling eels that use their teeth and suction to attach themselves to other fish and feed of their blood, an instrument was developed with similar teeth that fixate the morcellated tissue as it is inserted in the teeth-lined instrument. As such, it prevents the uncontrollable rotation of tissue fragments due to torque, thereby reducing tissue spillage.

Prospective Risk Inventory

In 2014, the *Leidraad Nieuwe Interventies in de Klinische Praktijk* was published by the *Orde van Medisch Specialisten* and the *Zorginstituut Nederland* with the support of the *Kennisinstituut van Medisch Specialisten*. [2] It aimed to structure the introduction of new technology into daily clinical practice to warrant safety, efficacy and cost-effectiveness, without raising thresholds for innovation.

A roadmap was created that emphasizes a careful consideration before the new technology is introduced. An important component of this roadmap is the prospective risk inventory (PRI). A PRI is an important item of a safety management system and intends to foresee risks in health care processes rather than to remedy adverse events after they have occurred.[34,35] No fixed model for a PRI is provided, since possible risks depend on specific situations and thus may vary per hospital. The range of the PRI procedure is defined by the associated risk of the technology and the frequency of its use.[2] (Figure 1) Low risk medical devices that are used on a large scale may still imply that a significant amount of patients may suffer from associated adverse effects. For instance, glucose meters appear to be low risk and easy to use. However, should these instruments malfunction or be misinterpreted the consequences may be detrimental if this leads to an overdose of insulin. The chance of this occurring may be small, however these instruments are widely used by diabetes patients and medical personnel. In contrast, high-risk medical devices that are used sporadically may not cause harm on a large scale, yet may cause severe damage to the individual. Power morcellators are an example of such high-risk devices. Both scenarios require an extensive PRI according to figure 1.

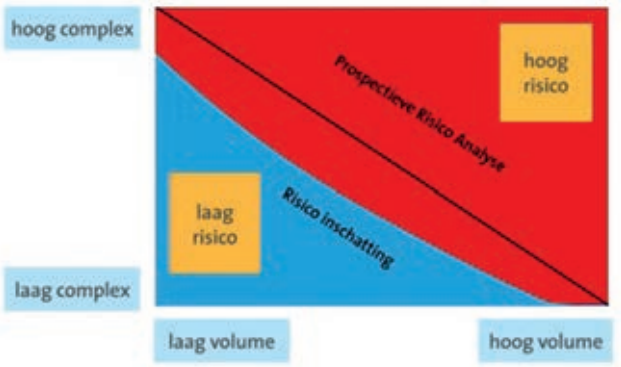

Figure 1: Relationship between risk and volume of a new technology and the range of a prospective risk inventory. (From: Leidraad Nieuwe Interventies in de Klinische Praktijk)

In this thesis, the concept of the PRI is applied to the morcellation issue as previously discussed. The high risk of encountering an unexpected uterine sarcoma led to the decision of the FDA discouraging the further use of power morcellators. It was previously calculated by the FDA that uterine sarcoma (US) and leiomyosarcoma (ULMS) may be present in 1 in 350 and 1 in 458 women undergoing hysterectomy or myomectomy for presumed benign fibroids respectively.[4] However this number has been criticized. It was calculated based on a limited number of studies which all consisted of data coming from referral centres.[36] Furthermore, high-risk patients were included (such as postmenopausal women and women with known malignancies) and varying definitions of sarcoma were used.[36] Recently the FDA has updated this risk of occult ULMS to 1 in 495 to 1 in 1100 women undergoing surgery, using data from more recent studies.[37] However, the initial FDA statement resulted in a worldwide decrease in the use of morcellators and in an increase in the number of laparotomies.[38-41] These outcomes appear to be in contrast to the advantages of MIS over laparotomy, which have been well established.[42] In fact, studies show morbidity and mortality in favour of MIS in most cases, even when including the accidental morcellation of uterine sarcoma.[43-46] However, the outcome in these prediction models strongly depend on the incidence of ULMS, making them difficult to use as long as this incidence is not better defined.

In **chapter 8**, we established the above mentioned risk of encountering unexpected ULMS during surgical procedures for presumed benign pathology. A nationwide cohort study was performed evaluating all ULMS diagnosed in The Netherlands between January 2000 and September 2015 using the database from the nationwide network and registry of histo- and cytopathology in The Netherlands (PALGA).[47] By using a nationwide database including secondary and tertiary health care centres the previous mentioned shortcomings of the number estimated by the FDA were eliminated. The risk of ULMS in women undergoing surgery was 1:385 or 0.26% for the whole group, and 1:795 or 0.13% for unexpected ULMS. Moreover, the risk for receiving non-standard treatment for ULMS (meaning abdominal hysterectomy with or without bilateral oophorectomy) in the unexpected group was even lower at 0.03% or 1:3333 patients. Using our results in the mentioned prediction models, it is shown that overall morbidity and mortality are in favour of laparoscopic procedures with morcellation as opposed to laparotomy procedures.[46] In addition, our study demonstrated that women aged 40-50 years of age presenting with abnormal uterine bleeding (AUB) are most at risk for unexpected ULMS. Unfortunately, this age group belongs to the age range with the highest ULMS incidence. Therefore in these women, the surgical approach to the removal of uterus or fibroids should be carefully considered. Reassuringly, in almost all postmenopausal women a ULMS was expected and consequently these women were at a low risk to undergo non-standard surgical treatment for ULMS. Finally, ULMS were very rare under

the age of 40 (only 4% of all ULMS cases). Therefore, minimally invasive or uterine sparing treatments could still be considered in these women.

To preserve the minimally invasive approach for the removal of uterus or fibroids, gynecologists are seeking to enhance the safety of power morcellation. In-bag morcellation is proposed as the *main* solution to the current safety issues and this technique appears to be promising. The results of in vitro tests regarding the efficacy of containing tissue are favourable and the clinical feasibility has been demonstrated.[30,48-50] However, long-term results are lacking and the oncological safety has yet to be proven. [51-54] In this light, results from in-bag morcellation techniques from other specialties should be considered. In urology it has been demonstrated that for low stage and low grade renal cell carcinoma laparoscopic nephrectomy with in-bag morcellation of the renal specimen appears to be a safe alternative to open radical nephrectomy. [55,56] However, there is evidence suggesting that this is not true for high stage/grade tumors (often displaying sarcoma-like characteristics).[57, 58] Given the aggressive nature of ULMS, in-bag morcellation should therefore be implemented with caution. Notwithstanding these limitations however, in-bag morcellation is currently nearly regarded as the gold standard for morcellation. As such, there is a risk that serious adverse events are overlooked and may reveal themselves in the future. In **Chapter 9** the rationale behind in-bag morcellation for myomectomy specimens was examined. It was hypothesized that tissue spillage occurs regardless of in-bag techniques. Leiomyosarcoma are heterogeneous tumours and malignant cells may be located anywhere in the leiyomyosarcoma, including at the cleavage plane used for myomectomy. Indeed, we demonstrated that myoma cells are spilled into the abdomen even before morcellation is performed. This observation has been substantiated in another study.[59] Therefore it can be concluded, that in-bag morcellation after myomectomy does not fully guarantee safety in case of unknown ULMS.

The PRI of in-bag morcellation was finalized in **chapter 10.** A Health Failure Mode and Effects analysis (HFMEA) was performed to prospectively identify moments in the morcellation procedure that are at risk for tissue spill.[60] The main finding was that although the spillage of larger particles can be avoided, the risk of spillage of small particles or microscopically amounts of spill remains due to contamination by instruments that came into contact with the morcellated tissue. Unfortunately, the clinical consequences of macro- versus micro-spillage are still unknown. For instance, in endometrial carcinoma the spread of malignant cells in the abdominal cavity via the fallopian tubes during hysteroscopy or dilation and curettage, does not appear to negatively influence the oncological outcome.[61-63] Yet, the negative impact of the morcellation of uterine sarcoma on the oncological outcome have been described, although not undisputable. [64] For instance, in one study characterized by a longer than average follow up, the

same recurrence rate was found in women with sarcoma confined to the uterus as in other studies with morcellated specimens.[65]

It should be questioned if our PRI would have revealed the adverse events of tissue spillage in its implemental phase in 1991. An important shortcoming exists of qualitative prospective methods such as the HFMEA. Insufficient knowledge of a procedure and the associated risks can lead to hazards not being identified or being over- or underestimated .[66,67] Recently, the FDA admitted its awareness of the possible spread of cancerous tissue when it approved the morcellation device.[68] However it was estimated that the chance of this occurring amounted between 1:1000 and 1:10.000 cases. Consequently this was not considered a significant risk. Already in 1997, only 2 years after the FDA approval of power morcellators, a report was published warning against the morcellation of undiagnosed malignancies.[69] In the following decade, similar studies were published on the topic, but up until 2014 these warnings were not acknowledged. Unfortunately, several developments were not considered in the initial risk estimation. For instance, uterus-sparing modalities are increasingly applied for the treatments of fibroids and abnormal uterine bleeding. One explanation for the surprisingly high incidence of ULMS in surgical specimens is, that as a result of this development nowadays only cases that are resistent to conservative treatment are treated surgically.[70] Furthermore, power morcellators have allowed the minimally invasive removal of increasingly large uteri, which previously would have been removed in total via laparotomy, thus the indications for a minimally invasive approach have extended.

Because of the limitations regarding risk estimations, it is suggested that an HFMEA is unsuited to study patient safety interventions.[67] However, the same study also demonstrated that the identification of hazards was valid and reproducible.[67] To overcome this flaw of underestimation of important hazards, the HFMEA method regards apparently small but possibly severe hazards as a “single point of weakness” that must be addressed before new technology can be implemented.[60] Another important critique is that the HFMEA is too time consuming and too demanding for hospital resources. Indeed, we spent over 12 hours discussing the in-bag morcellation procedure with 7 persons coming from 3 different departments of our hospital. In addition, time was spent to finalize the procedure via email. However, in our opinion the time that has been spent and is still spent on the morcellation subject since the FDA statement in 2014 quickly refutes this argument. Moreover, when patient safety is involved it should be questioned if too much time can be spent.

In all, it can be concluded that a timely PRI would perhaps not have resulted in a general warning regarding the spreading of cancerous cells, however it would have allowed a general awareness regarding this risk. With a more careful post-market surveillance,

early signs of adverse events may possibly have been taken seriously sooner. In addition, better insight in the actual incidence of ULMS would have alerted gynecologists to take caution when performing minimally invasive procedures in high-risk patients. Finally and most importantly, it would have allowed informed consent of the patient in the pre-operative workup. In a recent study it was demonstrated that patients were not averted from minimally invasive surgery when provided with information regarding the risks of morcellation during laparoscopic hysterectomy.[71]

Conclusion

The *clinically driven approach* to the development of new surgical instruments allows a close collaboration between clinicians and engineers. Several methods can be used to enhance a prototype before it is used on live humans for the first time. Surveys and literature reviews regarding instruments that resemble the proposed prototype are simple but effective tools to identify areas for improvement and gain insight in possible risks. Cheap and easily acquired materials such as beef tongue are valid models to assess favourable characteristics of new instruments. However proper models, including animal models, that resemble real-life circumstances are lacking in gynecology. Unfortunately, shortcomings regarding anatomical variations, the effects of freezing and thawing on tissue properties or the presence of pathology prevent human cadavers from becoming the gold standard model in stage 0 pre-human trials.

The prospective risk inventory offers a better understanding of a new procedure or surgical instrument and can therefore provide information regarding possible hazards. Performing an elaborate PRI is time consuming however. Since no strict guidelines exist regarding the extent and contents of the PRI and which procedures and instruments should be assessed, there may still remain a grey area where new instruments can escape a PRI before their implementation in daily clinical practice. Hospital-wide collaboration with respect to these aspects can eliminate this grey area and may reduce time by delegating tasks among this collaboration. To promote the sense of shared responsibility by hospitals, the implementation process could be organised into a so called “think-tank” where representatives of all hospitals participate. Recommendations derived from such a collaboration, can be swiftly applied in all hospitals without extensive additional scrutiny.

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Future Perspectives

It is clear that still much can be gained regarding patient safety during the development and implementation of new surgical instruments. The *clinically driven approach* as evaluated in this thesis resulted in a close collaboration between clinicians and engineers. This allowed quick feedback and input with respect to necessary modifications to the tested surgical instrument prototypes. Still, a large gap was discovered between the workings of new instruments in in-vitro models and their efficacy in human-like conditions. To close this gap, future research should focus on the development of easily accessible and life-like models. As such, 3D printed models are promising. However several shortcomings need to be addressed before they can successfully act as human-like models, mainly improving the resemblance to the natural compliance of human tissue. Enhancements in synthetics and biomaterials are therefore needed. Furthermore, virtual reality tools and computerized models can be valuable additions to *hands-on* testing of instruments, once these techniques are further improved to realistically reflect *real life* situations.

Regarding the power morcellator controversy, further research should be performed regarding the oncological effects of the spillage of microscopically small tissue fragments. Mouse models could provide a suited model to test the ability of a ULMS to metastasize via these spilled particles. The results of such research will finish the PRI of (in-bag) morcellation.

Several initiatives to further facilitate the *clinically driven approach* have already been installed. For instance, the University of Technology in Delft, The Netherlands has commenced a Bachelor of Clinical Technology, which aims to equip students with medical and technical knowledge, so they can form a link between technology and patients. Furthermore, a medical delta exists in the province of Zuid-Holland and the Twente region in which universities and colleges collaborate in health care innovations.

The next step in this collaboration would be the creation of centralized one-stop shops in hospitals where new innovations can be presented to a dedicated team who are educated to assess the safe implementation of the innovation in daily practice. These one-stop-shops should facilitate clinicians to present their innovations to engineers, thus providing an impetus to enhancing medical technology.

A *prospective risk inventory* should be an important item of this assessment, as its value was successfully demonstrated in this thesis. However, important questions need to be addressed. It is yet unclear if all innovations should undergo an elaborate PRI. Furthermore it is unclear who is responsible for the performance of a PRI: the manufacturer, engineer or physician. Since resources are limited, these are valid questions. It should

be attempted to coordinate a PRI as much as possible, to prevent several institutes performing the same procedure. To promote the sense of shared responsibility by hospitals, the implementation process could be organised into a so called “think-tank” where representatives of all hospitals participate. Recommendations derived from such a collaboration, can be swiftly applied in all hospitals without extensive additional scrutiny.

Finally, it should be realised that even with all the efforts as described in this thesis, hazards to patient safety cannot be fully eliminated. The purpose of a *clinically driven approach* and of a *prospective risk inventory* should be to reduce the number of possible hazards. To quickly identify residual hazards after the implementation of new instruments in clinical practice a post-market surveillance system should be installed. Currently, the registration of complications is only mandatory in research settings. In addition, this surveillance system should proactively intervene in case a trend is registered regarding an increase in adverse effects after a new instrument is implemented.

Finally, although not a research topic in this thesis, it is apparent that the safety of new surgical devices in daily clinical practice can only be warranted by proper handling. Therefore, education and training should be mandatory for every new user.

By identifying and reducing hazards before new technology is implemented together with an early identification of adverse effects after its implementation, a serious step can be taken to safer innovation in health care.