ÓBUDAI EGYETEM
ÓBUDA UNIVERSITY

NEUMANN JÁNOS

INFORMATIKAI KAR

SZAKDOLGOZAT

OE-NIK	Hallgató neve:	**Dr. Haidegger Tamás Péter**
2024	Hallgató törzskönyvi száma:	**T/008061/FI12904/N**

Óbudai Egyetem
Neumann János Informatikai Kar
Biomatika és Alkalmazott Mesterséges Intelligencia Intézet

SZAKDOLGOZAT FELADATLAP

Hallgató neve:	**Dr. Haidegger Tamás Péter**
Törzskönyvi száma:	T/008061/FI12904/N
Neptun kódja:	N8Q6A8

A dolgozat címe:

Technológiai érettség és értékelés sebészeti robotok esetében az MDR korában
Technology Readiness and Evaluation of Surgical Robots in the Advent of the MDR

Intézményi konzulens:	Prof. Dr. Gulácsi László
Külső konzulens:	
Beadási határidő:	2022. december 15.
A záróvizsga tárgyai:	Orvostechnikai eszközgyártás ipari minőségbiztosítás Orvostechnikai eszköz biztonság

A feladat

Az orvostechnika rohamos fejlődésével radikálisan új digitális eszközök jelentek meg a műtőben. A robotikának és az adattudományoknak minden bizonnyal radikális átalakító hatása lesz az invazív medicina egyes ágaira a következő 20 évben. A technológia önmagában azonban még nem minden, a klinikai eredmények javulását várjuk alkalmazásától. A klinikai értékelés módszereinek alkalmassá kell válnia a digitális sebészeti eszközök objektív mérésére is, hiszen a kép által vezetett sebészeti eszközöket és sebészrobotokat elsősorban pontosságuk és megbízhatóságuk miatt alkalmazzák. Ezen túlmutatóan, a teleoperációs Robot-asszisztált Minimál Invazív Sebészeti Rendszerek (RAMIS) esetében az aktív eszközök irányítását mindvégig a sebész végzi egy konzolon keresztül, emiatt csak indirekten támaszkodik a pre-operatív adatok integrációjára, vagy adatfúzióra, így ilyen esetekben a technológiát és a humán operátort együttesen kell tudni értékelni.
A világban eddig több tucat sebészrobotikai rendszert engedélyeztettek, alapvetően eltérő kialakítással és különböző beavatkozástípusokhoz. Ugyanakkor minden rendszernek hasonló fejlesztési és engedélyeztetési utat kellett bejárnia, amíg eljutott a TRL 9-es szintre. Az ezalatt gyűjtött klinikai bizonyítékok minősége és mennyisége radikálisan eltér az egyes robotrendszereknél. Mindez pedig szorosan kapcsolódik a fejlesztés és engedélyeztetés anyagi ráfordításaihoz, valamint gazdasági és klinikai értékeléséhez. A szakdolgozat témája ezen kapcsolatok és indikátorok objektív felmérése, elemzése.
A cél, hogy modellezni tudjuk a jövőben megjelenő újfajta technológiai komponenseket, pl., sebészeti döntéstámogató és hibakompenzációs rendszerek esetében a piacra jutás és a piaci validáció folyamatát, kiemelten az európai és az egyesült államokbeli engedélyeztetési eljárások tekintetében.

A dolgozatnak tartalmaznia kell:

- a robotsebészeti ágak, kiemelten a kereskedelmi rendszerek alapvető típusainak bemutatását,
- a kereskedelmi forgalomig eljutott rendszerek engedélyeztetési folyamatainak összefoglalóját (MDR és FDA viszonylatban),
- a TRL 9+ szintű aktív sebészrobotikai fejlesztések egy választott csoportjának klinikai evidencia eredményeit, típusonként (pl., EQ 5D value sets),
- a fenti csoport esetében a TRL 9+ szintű aktív fejlesztések anyagi ráfordításait,
- a fentiek modell szintű összevetését,
- analízist, konklúziót.

Ph.

ÓBUDAI EGYETEM * Neumann János Informatikai Kar * 1. Budapest

.....
Dr. Eigner György
intézetigazgató

A szakdolgozat elévülésének határideje: **2024. december 15.**
(OE TVSz 55.§ szerint)

A dolgozatot beadásra alkalmasnak tartom:

.....
külső konzulens

.....
intézményi konzulens

HALLGATÓI NYILATKOZAT

Alulírott Dr. Haidegger Tamás Péter hallgató kijelentem, hogy a szakdolgozat / diplomamunka saját munkám eredménye, a felhasznált szakirodalmat és eszközöket azonosíthatóan közöltem. Az elkészült szakdolgozatomban / diplomamunkámban található eredményeket az egyetem és a feladatot kiíró intézmény saját céljára térítés nélkül felhasználhatja.

Budapest, 2024. május 14.

Haidegger Tamás

.....

hallgató aláírása

ÓBUDAI EGYETEM
ÓBUDA UNIVERSITY

Neumann János Informatikai Kar

KONZULTÁCIÓS NAPLÓ

Hallgató neve:	Neptun Kód:	Tagozat:
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Szakdolgozat / Diplomamunka[1] címe magyarul:

Technológiai érettség és értékelés sebészeti robotok esetében az MDR korában

Szakdolgozat / Diplomamunka[2] címe angolul:

Technology Readiness and Evaluation of Surgical Robots in the Advent of the MDR

Intézményi konzulens:	Külső konzulens:
Prof. Dr. Gulácsi László	-

Kérjük, hogy az adatokat nyomtatott nagy betűkkel írja!

Alk.	Dátum	Tartalom	Aláírás
1.	2024.03.05.	Témavázlat és felépítés átbeszélése	
2.	2024.03.26.	Szakdolgozat struktúrájának kialakítása	
3.	2024.04.09.	Előzetes eredmények áttekintése	
4.	2024.04.23.	Szakmai anyagok áttekintése, prezentálás	

A Konzultációs naplót összesen 4 alkalommal, az egyes konzultációk alkalmával kell láttamoztatni bármelyik konzulenssel.

A hallgató a Szakdolgozat / Szakdolgozat I. / Szakdolgozat II. / Projektlabor 1 / Projektlabor 2 / Projektlabor 3 / Záródolgozati projekt / Diplomamunka I / Diplomamunka II / Diplomamunka III / Diplomamunka IV [3] tantárgy követelményét teljesítette, beszámolóra / védésre [4]bocsátható.

A konzulens által javasolt érdemjegy: Jeles (5)

Budapest, 2024. május 14

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Intézményi konzulens

1
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ABSZTRAKT

A robotika napjaink egyik megatrendjévé vált, amely újításaival megjelnik az életünk minden területén. Míg máig már több mint 300 sebészeti robot prototípust és műtéti rendszert fejlesztettek, ezek közül csak néhánynak sikerült kereskedelmi forgalomba kerülnie és még kevesebbnek szélesebb körben elterjednie, gazdasági sikert hozni. Az orvostechnikai eszközök a legszigorúbban szabályozott termékek közé tartozik a világon mindenhol, de különösen az Európai Unióban, miután 2021. májusában hatályba lépett az orvostechnikai eszközökről szóló Medical Device Regulation (MDR) rendelet. Ez jelentős kihívások elé állítja a gyártókat, különösen az alkalmazott mesterséges intelligencia és robotikai megoldásokat integráló fejlesztések esetében. A szakdolgozatom célja, hogy felmérje azokat a módszereket és eszközöket, amelyeken keresztül a CE-jelölés és az USA Élelmiszer- és Gyógyszerügyi Hatósága (FDA) típuskövetelményei szempontjából kezelhető az orvosi eszköztanúsítás összetett folyamata. A dolgozat szisztematikusan bemutatja a jelenlegi sebészeti robot osztályokat és kiemelkedő rendszereket, valamint a különböző értékelési módszerek elemzését adja ezek számszerűsítésére és összehasonlítására. Egy párhuzamosan lefolytatott kutatás eredményeit integrálva megállapítható, hogy az EQ-5D jelentési standardjainak követése döntő fontosságú lenne a sebészrobotika eredményeinek objektív értékeléséhez. Mivel a szakirodalomból hiányzott, megvizsgáltam a lehetséges statisztikai összefüggést a sebészeti robotrendszer fejlesztése és az engedélyeztetés, valamint a befolyt befektetési pénzek között. Míg szignifikáns összefüggések nem derültek ki, a kiválsztott 32 kiemelkedő sebészeti robotfejlesztő és gyártó cég adatainak szisztematikus elemzése rávilágított a befektetések időzítése, földrajzi elhelyezkedése és üzletnagysága közötti összefüggésekre.

ABSTRACT

Robotics is a megatrend of our times, entering all possible application domains. More than 300 surgical robot prototypes and commercial systems have already been developed, yet only a handful of them managed to achieve commercialization and a wider adoption, yielding to a commercial success. One of the anticipated hurdles that prevented many surgical robot systems from entering the market domains in time and yet with a high-quality setup, is the complexity of the conformity and compliance to the applicable standards. The European MDR presents significant challenges to manufacturers, especially in the domain of applied Artificial Intelligence and robotics. Among the MDR requirements there can be found the need to proove clinical benefit or non-inferiority, for which expensive trials, extensive literature review and health technology assessment procedures have to be initiated. The aim of this thesis work is to assess the methods and means through which the complex process of device certification can be managed from the European CE marking and the U.S. Food and Drug Administration (FDA) type requirements' point of view. The thesis systematically introduces the current surgical robot classes and outstanding systems, and provides the analysis of the various assessment methods to quantify and benchmark these. Integrating the results of a parallel research conducted, it can be concluded that following the reporting standards of EQ-5D would be crucial for the objective evaluation of the results. The possible correlation between surgical robot system development and clearance versus the collected investment money was investigated. While no significant correlation was revealed, the systematic analysis of the data of 32 outstanding surgical robot developer and manufacturer companies highlighted connections between the timing, geography and deal size of the investments provided.

TABLE OF CONTENTS

1 INTRODUCTION

The development of Robotics & Automation (R&A) and Artificial Intelligence (AI) methods in the past three decades resulted in the rise of entirely new application and control paradigms across various industries and domains, including medicine. Robotic devices have become common supporting patient care, providing rehabilitation or advancing diagnostics. Robotic systems, as Digital Medical Devices (DMD) are also directly involved in the execution of treatment plans in the Operating Rooms (OR), and since 1985, over 12 million successful robot-assisted surgical procedures have been accomplished worldwide. While hundreds of different prototypes and concepts are being developed globally, only a handful of systems have really been able to offer lasting benefits with respect to the patient and the operator, and even fewer became profitable as a business, having survived the rigorous regulatory and clearance procedures. Most surgical robot systems are considered high-risk DMD, where the main source of the hazard is the range of the autonomous functions implemented [1].

Traditionally, autonomy is considered as a fundamental component of robots, yet it is one of the hardest terms to define, assess and regulate [2]. It presents a great challenge within the medical field to quantify system autonomy and related safety and performance issues. The aim of this thesis work is to offer some cornerstones in capability assessment of surgical robots from the technology readiness point of view, and DMD maturity given the requirements of the authorities. This is the first known work aiming to match technology readiness and Health Technology Assessment (HTA) against financial investments on a system level. While safety and efficacy remain the most important factors for the evaluation of surgical systems, more recently, sustainability of robotics has also become a major topic, bringing together social responsibility with technical excellence and the United Nations (UN) endorsed sustainability goals [3].

The importance of technology assessment, value quantification and standardization has become paramount in the medical domain since that is the primary way to increase safety systematically—through standardized testing requirements and protocols. This is an actively researched area in many centers, including the University Research and Innovation Center (EKIK) at Óbuda University (OU) [4].

Further aim of this thesis work is to offer an initial insight and estimation of the complexities brought to the regulatory and clearance procedures of surgical robots through the recent changes in the procedures, especially with respect to the Medical Device Regulation 2017/745 (MDR) in Europe. My work was to collect available public data on well established and emerging surgical robot companies and their systems, both in the prototype level, and in the commercial phase. Then I assessed their Technology Readiness Levels (TRLs), the available proof for their efficacy (through HTA, where applicable), and compare the data to the total amount of funding received for the project, wherever there was available data.

2 FUNDAMENTALS OF SURGICAL ROBOTICS

2.1 Categorization of surgical robots

Surgical robots belong to the wider class of systems under Computer-Integrated Surgery (CIS), and often referred to as interventional systems. “CIS is the most commonly used term to cover the entire field of interventional medical technologies, from medical image guidance and augmented reality applications to automated tissue ablation” [5,30].

Technically, almost all surgical robot systems have a common feature, they employ a robotic mechanism (robot in the widest sense [6]) to provide accurate guidance, assistance or direct delivery of instruments or energy. The meaning of “robotic device” can be defined in the generic International Organization for Standardization (ISO) sense, according to which industrial robots are pre-programmed, with multiple Degrees of Freedom (DoF), physically moving in their space and executing tasks. Such systems can focus energy, as in radiotherapy or High Intensity Focused Ultrasound (HIFU) treatment for example, or steer needles and other tools. These DMDs typically rely on precise pre-operative planning, performed on patient imaging information usually using 3D modalities like Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) [5].

Basically, there are two distinct control approaches that prevailed for surgical robot systems. Telesurgical robotics, as a technical solution has become the first domain within medico-surgical robotics that achieved a true global clinical adoption, and since 2022, we even have clinical systems working in Hungary as well [7]. In the meanwhile, several classes of surgical or interventional robots also appeared in clinical use, with different architectures [8]. A traditional domain of application is where the robotic execution of a predefined surgical plan relies on medical imaging, thus called image-guided interventional robotics (discussed under Section 2.2), while collaborative control is also a popular choice [1], especially in neuro and orthopedic applications, it is not discussed separately in this thesis.

Microsurgical systems and endoluminal robots are also present on the market, and despite the fact that they share a lot with telesurgery systems in terms of mechatronics, control architecture and future perspectives (sometimes even the physical platform is shared, as in the case of the single port da Vinci SP (Intuitive Inc., Sunnyvale, CA) [9])—these are considered together with their respected field determined by their control (human–machine interface) approaches.

To a large extent, with respect to efficacy, interventional robotic systems can be assessed by how they reconcile the pre-operative plan with the intraoperative reality, and whether/how they cope with tissue motion and deformations during the procedure [5]. Such capabilities assume a certain level of actuation and control of the robot, as well as a

high-level interface or cooperation with the physician. Several taxonomies have been used to describe interventional robots, most of them agreeing on a classification related to the level of interaction between the robot and the user when producing a movement. These taxonomy classes can be active, passive, teleoperated and shared-actuation (or co-manipulated) robots. An active robot is being able to move instruments in the OR on its own (in a pre-programmed manner), whilst being supervised by an operator and requiring discrete actions from the operator (such as confirmation of critical steps). Passive arms (sometimes called passive robots) are most often unactuated mechanical arms, able to hold an instrument, and to provide its position (see for instance radiotherapy applications [10]). Passive arms, where the user holds the instrument and provides the actuation, require continuous action from the human operator to carry out the intervention. Teleoperated robots are actuated systems, holding and moving instruments, but they are remotely controlled in real-time by a human operator, and are endowed with only very limited autonomous capabilities (such as tremor filtering).

A variety of robots involve “shared actuation” scenario, where the human operator and the machine both hold the same instrument, and their intents are communicated to each another by applying and sensing force on the tool, a.k.a. force control. Teleoperated systems can further benefit from a priori anatomical information through the concept of cooperative control, where the surgeon is actually guiding the tool physically.

The robot may constrain the task kinematically through appropriate hardware design, such as enforcing linear, planar or conical motions, in a scenario typically referred to as “semi-active” [11]. Constraints may also be programmable and implemented using passive constraints [12] or active constraints (a.k.a. virtual fixtures [13].) The systems with programmable constraints go with several names, they are often referred to as co-manipulated or hands-on or synergistic systems [14]. This means a hybrid control architecture, where the mechatronic system can impose physical, spatially defined Virtual Fixtures on the motion of the robot’s applied part and allows for further safety and autonomous functions. For instance, this has been successfully implemented in retinal microsurgery with the Steady Hand system at the Johns Hopkins University [15].

Active and co-manipulated robots require a planning phase to specify the task to be executed. Conversely, passive and standard teleoperated robots do not strictly apply explicit path planning (beyond what the traditional surgical plan means), since the operator always stays cognitively in the control loop. However, in the advent of surgical automation and subtask level autonomy, even for these types of systems, more sophisticated guidance may be required, such as pre-operative planning [1]. A common issue to planning-based robots is the need to relate the intra-operative pose of the target to the pose of the robot, also known as “robot registration” issue. Often based on image registration and calibration approaches, it remains an obstacle to clinical translation. When the target moves due to the intervention itself or to physiological activity (heart beating, breathing, etc.) more sophisticated approaches are required, such as visual

servoing or model-based real-time re-planning [16]. Such a high level of real-time automation unavoidably raises safety issues [1], evoking ethical and system design methodology question.

2.2 Robot-Assissted Minimally Invasive Surgery (RAMIS)

RAMIS classification only includes full-scale, teleoperational surgical systems, where the end effector typically does not require snake-like complex (6++) Degrees of Freedom (DoF) articulation. Most recognizable system is the absolutely market-dominating da Vinci Surgical System (Intuitive Inc, Sunnyvale, CA), which has seen 5 generations already since its debut in 1998 (Fig. 2.1).

Their relative success (still at a low single-digit percentile as per total market penetration) roots in the human-in-the-loop control, wherein the trained surgeon is always kept responsible for the clinical outcome achieved by the robot-actuated invasive tools. Nowadays, this paradigm is challenged by the need for improved surgical performance, traceability and safety reaching beyond the human capabilities. Partially due to the technical complexity and the financial burden, the adoption of telesurgical robotics has not reached its full potential, by far. Apart from the da Vinci, there are already over 65 emerging RAMIS robot systems, out of which 16 have already achieved some form of regulatory clearance (Fig. 2.2) [17]. My work aims to connect the technological advancement with the principals of commercialization and clearance procedures, particularly looking at investment attracted. While the regulatory requirements and foundational standards seldom change or see an update, there can be a continuous push for cutting edge development from market-oriented companies, aiming to monetize their unique technologies. Computer-assistance is gradually gaining more significance within emerging RAMIS systems, many times, commercial success is rather a combination of technical expertise, professional skills, funding and luck.

2.1. Figure: The flagship of the RAMIS systems, the newest generation da Vinci 5 from Intuitive with the redesigned surgeon cockpit and the patient-side manipulators. (Image credit: Intuititve Inc.)

RAMIS relies on real-time imaging, using an endoscopic camera, which can provide a wide angle, high resolution, white-light, video stream as the main sensory feedback from the surgical site. The robotically articulated instruments are maneuvered by the surgeon, through a surgical console i.e., human–machine interface, who controls based on the video stream. This synergy of the minimally invasive paradigm shift has been a catalyst for the use of robotic assistance, and has grown rapidly over the past decade, as reflected by the annual 2.3 million procedures (with a 15% annual growth) performed last year using the da Vinci alone, making it by far the most popular RAMIS system to date. The main factors that contributed to the outstanding success of da Vinci and its telerobotic concept include [17]:

- Advanced technology features, including better vision and instrumentation;
- Ergonomics and safety (EndoWrist for suturing, tremor filtering, improved situation awareness);
- Strong evidence for improved patient outcome collected over the years;
- Targeting procedures, where the quality of life can be improved significantly (prostatectomy, benign hysterectomy, etc.);
- Strong training program developed over the years (including simulators);
- No high-level autonomy introduced, therefore the legal responsibility remained with the surgeon;
- Massive marketing and promotion;
- Solution selling (consumable and service-based business model).

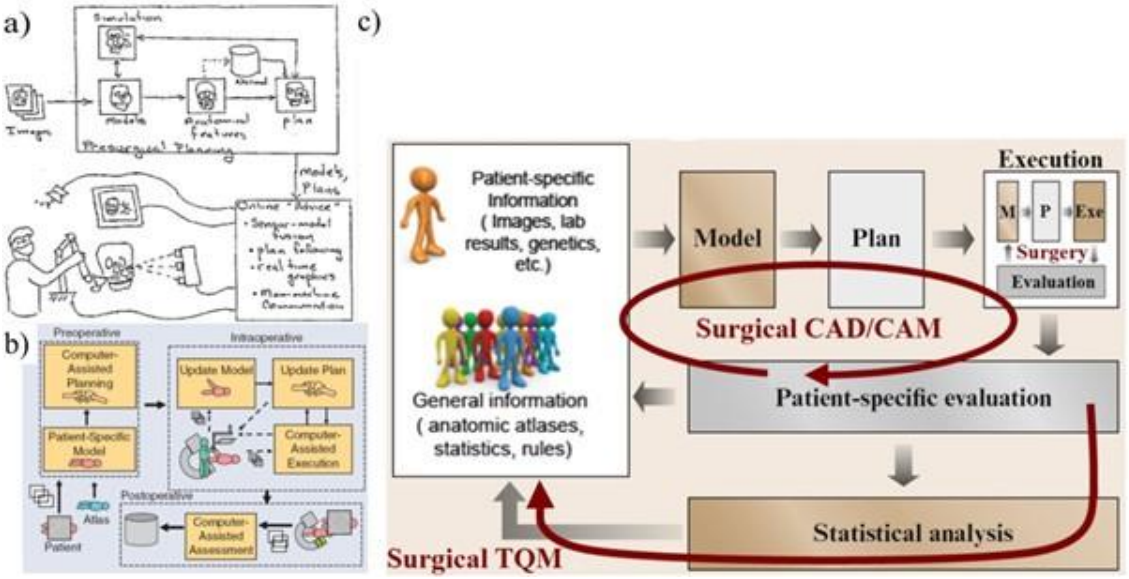
The popularity and acceptance of the da Vinci technology grows continuously, even in Hungary, as shown by our most recent poll-based assessment [18]. 54% of the interviewed people would have chosen robotic and robot-assisted surgeries over a conventional one in a hypothetical surgical scenario.

2.3 Image-guided surgical robots – CAD/CAM paradigm

A large family of CIS procedures can be represented by a model analogous to traditional industrial manufacturing systems. If proper pre-operative information is available, the intervention can be pre-planned ahead of time (offline, outside the OR), and executed in a reasonably predictable manner (involving some sort of intra-operative tracking for data registration and fusion [19,20]). Traditionally, such robots can be classified as surgical Computer-Aided Design (CAD) / Computer-Aided Manufacturing (CAM) systems (Fig. 2.3) [8]. In Surgical CAD, series of pre-operative medical images, statistical models, atlases and other information are pre-operatively combined to model an individual patient; the computer then assists the physician in planning an appropriate intervention (this may happen to be built into a medical imaging system).

2.2. Figure: The most advanced RAMIS systems, featuring only commercially available, and ready-to-launch platforms, already cleared for at least a limited set of surgical indications (presented in the order of time of appearance). A) da Vinci Xi, b) Senhance Surgical Robotic System c) Revo-i, d) Versius, e) avatera, f) hinotori, g) Dexter, h) Symani Surgical System, i) Toumai Endoscopic Robot, j) Mantra, k) Hugo RAS System, l) Bitrack. Table I provides details regarding these robots' basic engineering and clinical capabilities [17].

In Surgical CAM, intra-operative medical images and additional sensor data are used in the OR to register the pre-operative plan to the actual patient. The model and the plan are updated throughout the procedure, while the physician performs the procedure using appropriate technology, such as optical guidance, perceptual guidance and, most interestingly for this paper, some robotic device. Post-operatively, the computer can play a crucially important role in reducing procedural errors (quality management), and in promoting consistent and improved delivery of the treatment (quality assurance). Procedural outcomes can be captured in statistical models and fed back into the system for planning and optimizing subsequent procedures, which should foster evidence-based medicine in the context of human interventions [7].



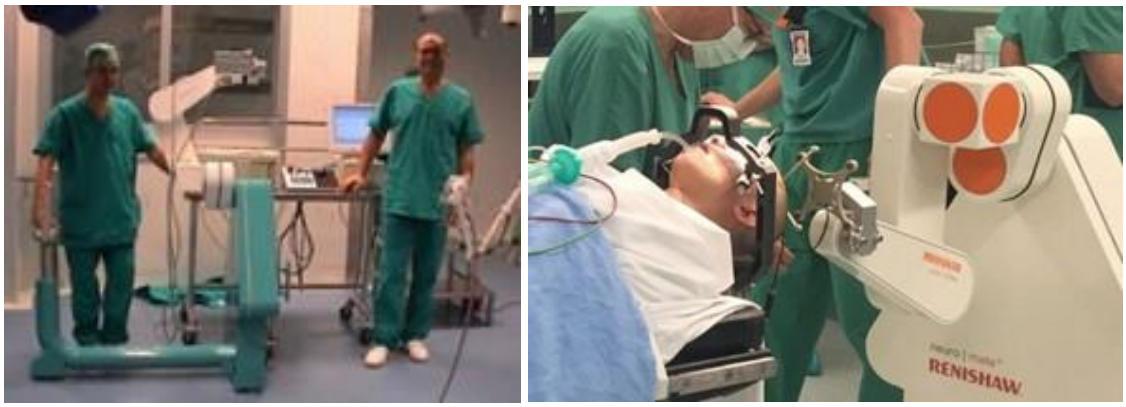
2.3. Figure: The traditional Surgical Computer-Aided Design / Computer-Aided Manufacturing (CAD/CAM) model, as a) first presented in 1993 [21]; b) then in digital in 2003 [22]; c) a more recent version, including the concept of Total Quality Management (TQM) in surgery in 2016 [7].

The concept proved to be a remarkably durable throughout the three decades of evolution of the field. Numerous technological innovations have improved upon all underlying system components, yet the original paradigm remains largely valid. Moreover, assuming very rapid control cycles, the *Model – Plan – Execute – Evaluate* even fits teleoperation-type RAMIS systems like da Vinci [1].

Image guidance can also help with numerous other surgical domains, where the anatomy allows for more precise registration, such as in neurosurgery or ophthalmology [23]. Specific surgical setups that made it to advanced prototype level are listed in Table II (at the end of the document).

It is well understood that the additional pre-operative or intra-operative information available, e.g., through imaging, may largely help to improve the spatial treatment accuracy, including the procedures performed as RAMIS. Prototype da Vinci setups have already demonstrated capabilities of patient-relative localization and other spatial navigation features [10].

One of the pioneering Surgical CAD/CAM systems was the neuromate, conceived in Grenoble by a group of pioneers who made seminal contributions to the field (Fig. 2.4) [24]. While in industrial manufacturing, CAD/CAM suggests uniformly designed parts and perfectly streamlined processes, human patients exhibit a huge variability to the point, where augmenting and guiding human tasks becomes extremely challenging technically and may affect the safety of the procedures involved. This poses significant challenges when introducing autonomy to surgical execution.



2.4. Figure: a) The first clinically used (1998) and b) the current, commercially available version of the neuromate robot being set up for stereotactic brain biopsy. (Credit: Renishaw plc.)

3 HEALTH TECHNOLOGY ASSESSMENT FOR MEDICAL DEVICES

There sections are under embargo - temporarily

4 ASSESSMENT OF SURGICAL ROBOT SYSTEMS

4.1 Digital Health and Technology Assessment

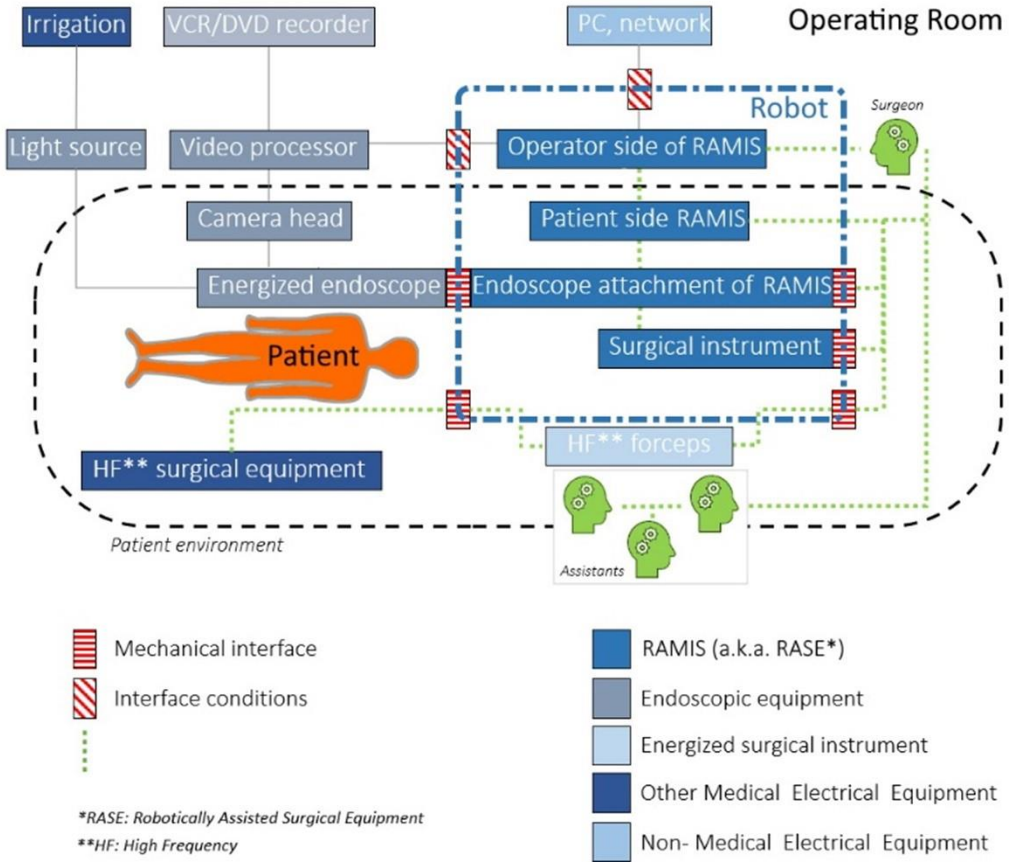
There sections are under embargo - temporarily

5 STANDARDIZATION AND REGULATORY PROCEDURES

5.1 International standards supporting the surgical robotics domain

In 2015, the ISO Technical Committee 299 Robotics began its work on a new standard, setting out basic safety and operational requirements for surgical robots [7]. As a direct outcome, in 2019, a new standard was published under the auspices of the International Electrotechnical Commission (IEC), detailing requirements for the basic safety and essential performance of robotically assisted surgical devices. Despite being a relatively simple and limited scope, this standard can inform bodies to establish the necessary link between the safety of MEE/MES and robotic systems [51]. These can help to create and maintain a Total Quality Management (TQM) approach in digital medical device development.

The two main technical SDOs, the ISO and the IEC have been working on these issues for a long period of time. Apart from ISO 13485:2016 - Quality management systems and the IEC 60601-1 – Medical electrical equipment, general standards of the domain, more specific recommendations appeared recently, in the form of the IEC/TR 60601-4-1: Medical electrical equipment – Part 4-1: Guidance and interpretation – Medical electrical equipment and medical electrical systems employing a degree of autonomy and the IEC 80601-2-77: Particular requirements for the basic safety and essential performance of robotically assisted surgical equipment [54]. These new standards bridge the gap between the traditional approach of treating medical devices (i.e., Medical Electrical Equipment (MEE) and Medical Electrical Systems (MES) in the standard's taxonomy) separate from robots (falling under the machinery directives). It has been clearly defined that an MEE/MES can be a robot, while still being regulated as a medical device, with a certain degree of autonomy. This ends the confusion around RAMIS, which are clearly robotic systems, despite the fact that all of the known devices got cleared by FDA in the 510(k) process, providing that they are "substantially equivalent" to something already cleared and existent, such as the da Vinci being regulated as an endoscope holder, a "surgical system, computer-controlled instrument". The standards establish the necessary mappings and correlations between the robotic components and the traditional medical device nomenclature (Fig. 5.1).



5.1. Figure: The ISO/IEC standard concept of RAMIS components and interfaces linking the robotic parts to the other medical devices (MEE/MES) in the OR. (Modified from [51].)

5.2 Procedures at FDA and MDR level

The single most important factor is patient safety, when it comes to medical robot clearance. Both the US FDA and the sustaining processes of the European CE mark render the responsibility largely to the manufacturer, expecting significant amount of management, documentation and quality assurance work in the background. To support this, medical device manufacturers typically have implemented entire quality policies and adequate processes.

It has to be noted that since separate approval is required for each intended clinical domain use of a surgical system, the approach and timeline chosen by the manufacturer may fundamentally determine the pathway the system may take [55]. In this thesis I aimed at identifying some correlations between the outcome, time and money invested into regulatory processes.

International standardization of medical devices facilitates the market access for new medical products, helps to overcome technical barriers to international trade, and supports market growth. While legislation and product safety regulations are the primary basis for

creating specific product types that contribute to the creation of new markets, industry standards (international guidelines and recommendations) can help reduce safety risks for users (patients, doctors and professionals) and reduce the risk of manufacturer liability [56].

For a long time, it was not clear whether medical robots should be considered robots at all, and some manufacturers were explicitly reluctant to refer to them as such. By doing so, they hope to stay clear of the relevant ISO technical standards and to avoid the FDA Pre-Market Approval (PMA) route and the European Machinery Directive 2006/42/EC, both being regulations that meant to prevent hazards introduced by robots into the operating room [17]. In its robotics standards, ISO consistently excludes medical devices, stating that they fall under other product classifications: the IEC-60601 family, describing the safety and performance requirements for MEE&MES (now in preparation for the 4th Edition) [57].

5.3 The U.S. FDA

The North American market presents definitely the biggest opportunity for digital medical devices. Currently available robots on the U.S. market went through the Food and Drug Administration's 510(k) clearance pathway, where the substantial equivalence to an approved device has to be demonstrated. This means, manufacturers were reluctant to implement new (e.g., autonomous) features in their systems. They rather not claim them "robots", fearing that the FDA might divert them to the more stringent Premarket Approval (PMA) regulatory process. The difference might be significant; on average, to get 510(k) clearance costs $31 million and 10 months, while the PMA takes $94 million and 54 months [58]. The procedures both in Europe and in the U.S. are focusing on the safety and transparency of medical devices, as FDA also shares the view that medical robots are only different from other robots in terms of "intended use" [59].

FDA's Center for Devices and Radiological Health (CDRH) recognizes these unique considerations and released an action plan for R&A devices in 2021, putting an emphasis on the commitment to transparency and usability [60]: "*FDA is reviewing an increasing number of applications for R&A devices, with the number receiving FDA marketing authorization nearing seven hundred as of October 2023. R&A devices have unique considerations during their development and use, including those for usability, equity of access, management of performance bias, the potential for continuous learning and stakeholder (manufacturer, patient, caregiver, healthcare provider, etc.) accountability. These considerations impact not only the responsible development and use of R&A devices but also the regulation of such devices.*" Transparency of AI systems is a critical cornerstone of the European AI Act as well.

5.4 The new timeline of the European MDR

Products in the regulated categories, such as surgical robots, shall comply with the relevant standards and bear the CE marking to demonstrate conformity.

Strict regulations apply to Class II and Class III category medical devices, which got much more rigorous in Europe, due to the recent EU Medical Device Regulation (MDR) (EU 2017/745) [61]. The new regulation significantly increased safety-related expectations and the requisite documentation for certifying medical devices, disproportionately affecting medical robots. The transition period began in May 2017. The acquisition of new certificates and the extension of the credentials was only be possible until May 2021. (Extended due to the COVID-19 pandemic). New products must yet comply with the MDR, while products certified under the MDD can still be marketed until 2024 (exceptions will be made if we introduce a major change to a product, in which case we may still have to certify under the new MDR before 2024.) From 2024, all products must comply with the requirements of the MDR, since it is a regulation, there are no adaptations and cannot be any deviations.

European guidelines, directives and regulations are a single certification procedure in the EU [62,63]. Recent update of the transition timelines led to EU MDR Transition Timelines extensions:

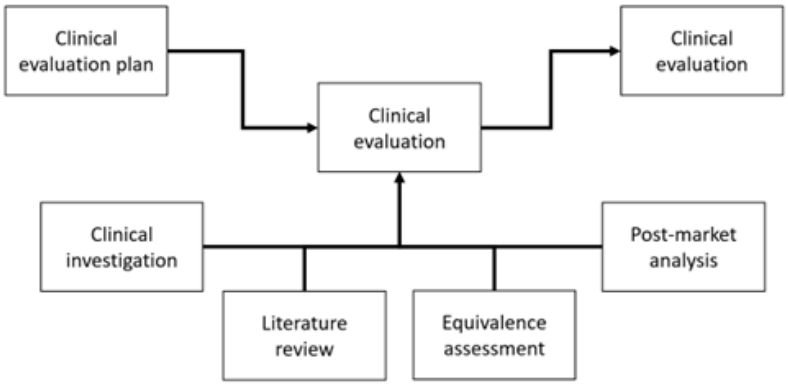
- until 31st December 2027. for Class IIb and III;
    - until 31st December 2028. for Class I and IIa;
    - until 26th May 2026. for Class III Implantable customer-made devices;
    - extends validity of certificates issued up to 26 May 2021.

5.5 The role of literature review and compliance analysis

Under the MDR, new devices shall go through "evidence-based investigation" – through which the clinical equivalence must be examined. Relevant requirements from the Directive include (Fig. 5.2):

- *„clinical evidence*: means clinical data and clinical evaluation results pertaining to a device of a sufficient amount and quality to allow a qualified assessment of whether the device is safe and achieves the intended clinical benefit(s), when used as intended by the manufacturer;
- *clinical evaluation* means a systematic and planned process to continuously generate, collect, analyse and assess the clinical data pertaining to a device in order to verify the safety and performance, including clinical benefits, of the device when used as intended by the manufacturer;

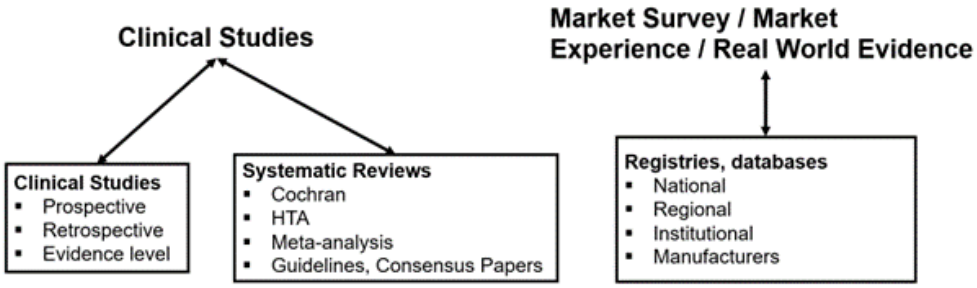
- *clinical investigation* means any systematic investigation involving one or more human subjects, undertaken to assess the safety or performance of a device;
- *clinical investigation plan* means a document that describes the rationale, objectives, design, methodology, monitoring, statistical considerations, organisation and conduct of a clinical investigation;
- *clinical data* means information concerning safety or performance that is generated from the use of a device and is sourced from the following:
- clinical investigation(s) of the device concerned,
- clinical investigation(s) or other studies reported in scientific literature, of a device for which equivalence to the device in question can be demonstrated,
- reports published in peer reviewed scientific literature on other clinical experience of either the device in question or a device for which equivalence to the device in question can be demonstrated,
- clinically relevant information coming from post-market surveillance, in particular the post-market clinical follow-up." [61].



5.2. Figure: The role of literature review and compliance analysis: This illustrated new process is one possible way of the clinical investigation, to ensure compliance.

MDR's Chapter VI. describes how the manufacturer should execute the Clinical Evaluation and Clinical Investigations. The main idea behind – and the action items for the manufacturer is coming from these sections. The manufacturer therefore has to perform a systematic literature review, do the necessary requirement engineering and collect and accumulated deep knowledge about all parts of the device (Fig. 5.3):

"The manufacturer shall specify and justify the level of clinical evidence necessary to demonstrate conformity with the relevant general safety and performance requirements. That level of clinical evidence shall be appropriate in view of the characteristics of the device and its intended purpose." (MDR Article 61.)



5.3. Figure: Level of evidence on your own device – first and most important stage: identification of pertinent data.

5.6 The role of AI and the compliance with the MDR and good practices

EU MDR and the In-vitro Diagnostic Medical Devices Regulation (EU) 2017/746 (EU IVDR) in combination with the General Data Protection Regulation (EU) 2016/679 (GDPR) contain requirements for AI in healthcare to be safe and performant. These requirements, both ex ante and ex post requirements, ensure medical devices based on artificial intelligence are safe and performant throughout their entire lifecycle [57,62]. The MDR requires in general that the R&AI application regulated shall be:

- SAFE during whole lifetime;
- TRANSPARENT from decision making point of view;
- AI methods coming together with data;
- Pre-determined changes in algorithms must be possible to fine tune based on new data;
- Supporting the AI to learn from data or experience (online or offline).

It has to be noted with care, that AI may change its model during runtime through self-learning. Such hard challenges pose significant headache to digital medical device manufacturers [64]. To deal with such versatility, systematic and ethical-responsible system design is also required. A recent IEEE initiative formulated the Ethically Aligned Design principle, which has become an international standard (IEEE 7000 - IEEE Model Process for Addressing Ethical Concerns During System Design; https://ethicsinaction.ieee.org) [65,66].

6 RESULTS OF LANDSCAPE SCOUTING

6.1 State of the Art in surgical robotics

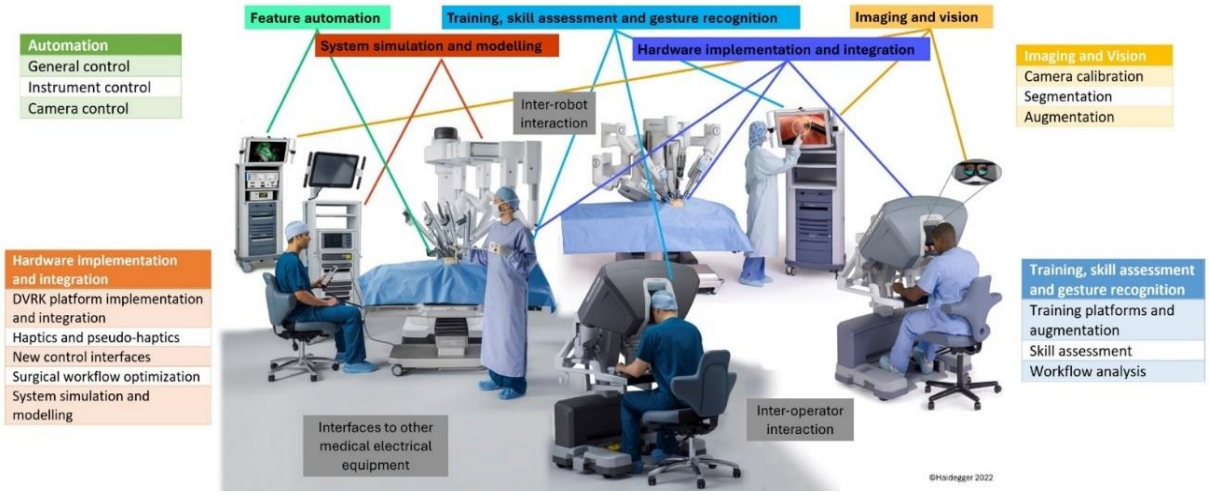
In recent scoping literature review, I identified over 65 documented research projects aimed at developing new, complete RAMIS systems, while my current complete records (raw research data) enlist a total of 302 projects and prototypes [7,17]. Yet, out of those, only 16 RAMIS managed to acquire some national clearance, and only 5 achieved sales in more than one country (Fig. 2). Table I includes a list of known, recognized RAMIS systems at the Technology Readiness Level 9+. A recent review by Moglia et al. covered the types and variations of these systems [67]. Another recent systematic review by Dupont et al. pointed out initial efforts on the development of surgical automation and the integration of force sensing into laparoscopic tools as probably the most important upgrade if the past decade, along with the novel robot architectures aiming to reduce procedural invasiveness [68].

On the research platform side, the most notable recent achievement is arguably the da Vinci Research Kit (DVRK), an open hardware and software platform created by the Laboratory for Computational Sensing and Robotics (LCSR) at Johns Hopkins University (JHU), Worcester Polytechnic Institute (WPI) and partners, supported by Intuitive Foundation (*https://www.intuitive-foundation.org/dvrk/*) [69,70]. More than 40 university groups and research centers are in the program, using retired classic da Vinci Surgical Systems as repurposed, re-assembled research platforms, capable of exploring innovative new concepts in RAMIS (Fig. 6.1). A recent review by D'Ettore et al. collected the most relevant projects with the platform [10].

Current research efforts on the DVRK can be considered as good proxies for RAMIS development directions, and can be categorized as (Fig. 6.1):

- Hardware implementation and integration;
- System simulation and modelling;
- Imaging and vision;
- Feature automation;
- Training, skill assessment and gesture recognition.

In most of the identified research topics, access to data with the DVRK is seen as a key enabling factor. Both kinematic or system data derived from the robot, or clinical data acquired through the vision system, is paving the way for the application of data-driven Machine Learning (ML) and AI methods.



6.1. Figure: The applied research directions on RAMIS systems already established, based on the first 10 years of DVRK related projects. Initial focus was mostly on hardware capabilities and component analysis, while more recently, much attention is paid to software enhancements, decision support and autonomous function development [26]

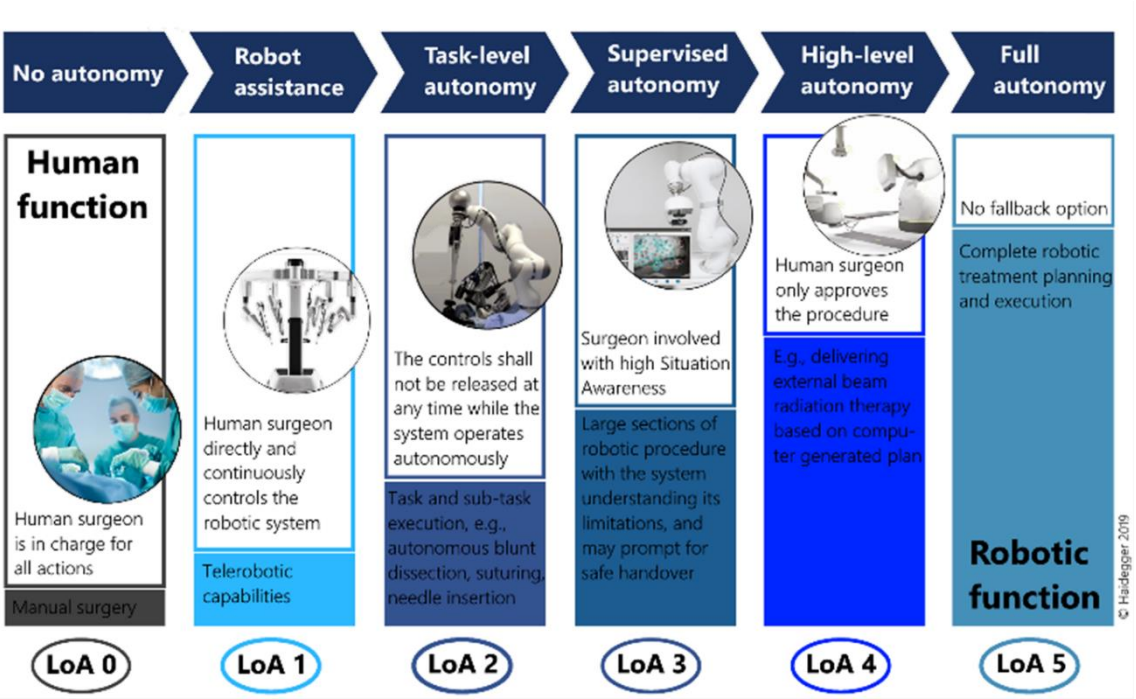
6.2 Autonomy, the distinguishing factor

Autonomy is probably the most important feature related to the applicability of a robotic system. Medical robotics also started to employ the Level of Autonomy (LoA) concept (originally proposed for the automotive industry), which helps to identify and compare system functions and capabilities [71]. It builds on the classical model of analyzing tasks and decisions along the Generate–Model–Plan–Execute cycle, an overarching autonomy concept from industrial robotics [72] to image-guided interventional systems [7]. The classical Surgical CAD/CAM (Computer Aided Design/Manufacturing) control flowchart is technically applicable even to RAMIS systems—assuming a very high control loop frequency. This means that the fundamental concept that digital information enables accountable, measurable system engineering and quality management concepts in CIS through medical imaging, image processing and robotic execution is completely valid in the case of RAMIS as well [17].

Fig. 6.2 presents the most recent classification of LoA of surgical robots [1], where current RAMIS systems reside at LoA 1, LoA 2 at the most. While the standardization experts still argue what degree of autonomy to be considered as a minimum requirement regarding “robots” in general [6], undoubtedly, the direction of development is towards achieving higher LoAs through improved autonomy, driven by a technology push and an economic pull.

Current successful approaches focus on sub-task and task-level automation in RAMIS, allowing surgeons to better focus on the critical parts of their procedures [73].

New RAMIS research concepts are emerging on the system side, in the form of miniaturization, complete systems are being down-sized for microsurgery, while there are other robot-ensemble and robot swarm prototypes being considered [74].



6.2. Figure: The concept of Level of Autonomy (LoA) classification in RAMIS, where current teleoperational systems reach only LoA 1 typically, providing assistance with basic safety support under remote control [1].

6.3 The AI component

The Surgical CAD/CAM model does not aim to eliminate the human surgeon from the interventional process, nor it assumes a uniform patient, anatomy, or disease. The pre-operative planning is always specific to the patient, and usually involves some clinical judgement. Then, for many types of interventions, the rest of the procedure can be carried out with little or no human touch. The extreme example is stereotactic radiosurgery (performed with. e.g., the CyberKnife robotic system [75]), which can be fully automated, all the way, from target identification to delivery of the therapeutic dose. Such autonomous function gained significant boost from recent development in R&A advancements, yet pose a significant challenge to regulatory bodies to ensure product safety.

The development and application of ML methods in robot-assisted surgeries requires well-defined criteria for validation [65, 66, 76]. In addition, methods that can deal with data heterogeneity as well as sparsity and real-time capability are needed [77]. This requires real-time control and novel communication networks, with a low latency and a

high resilience in the OR. Especially in surgical applications explainability and transparency are important aspects, research areas within AI that have just recently gained attention [17]. According to the *Data-driven research framework for a trustworthy AI* (DaRe4TAI) group [78], a system shall have the properties of:

- Beneficience;
- Non-maleficience;
- Autonomy;
- Being just;
- Explicability.

Dealing with all of the above, the subject of AI governance is actively debated these days, not only the EU and US government bodies are looking for formalized solutions, but also a set of emerging standards from ISO and IEC target this domain (including healthcare and robotics among their target application areas), such as [17]:

- ISO / IEC CD 23894.2 ISO JTC 1 / SC 42 / WG 3 Information Technology - Artificial intelligence - Risk management;
- ISO / IEC NP TS 8200 Information technology - Artificial intelligence - Controllability of automated artificial intelligence systems
- ISO / IEC TS 4213: 2021 Information Technology - Artificial Intelligence - Assessment of machine learning classification performance;
- IEEE 7000-2021 - IEEE Model Process for Addressing Ethical Concerns During System Design. Ethically Aligned Design project (*https://ethicsinaction.ieee.org*);
- IEEE 7007-2021 - IEEE Ontological Standard for Ethically Driven Robotics and Automation Systems [64].

7 ECONOMIC RATIONALE OF TECHNOLOGY INVESTMENTS

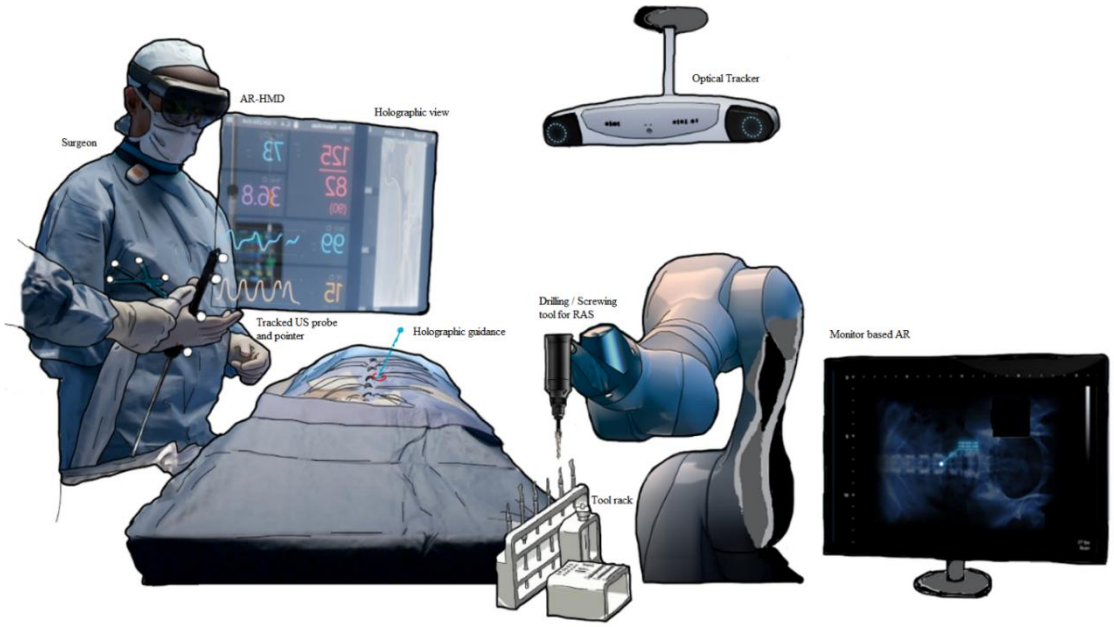
7.1 Financial and business case considerations

There sections are under embargo - temporarily

8 ACCOMODATING FUTURE TRENDS

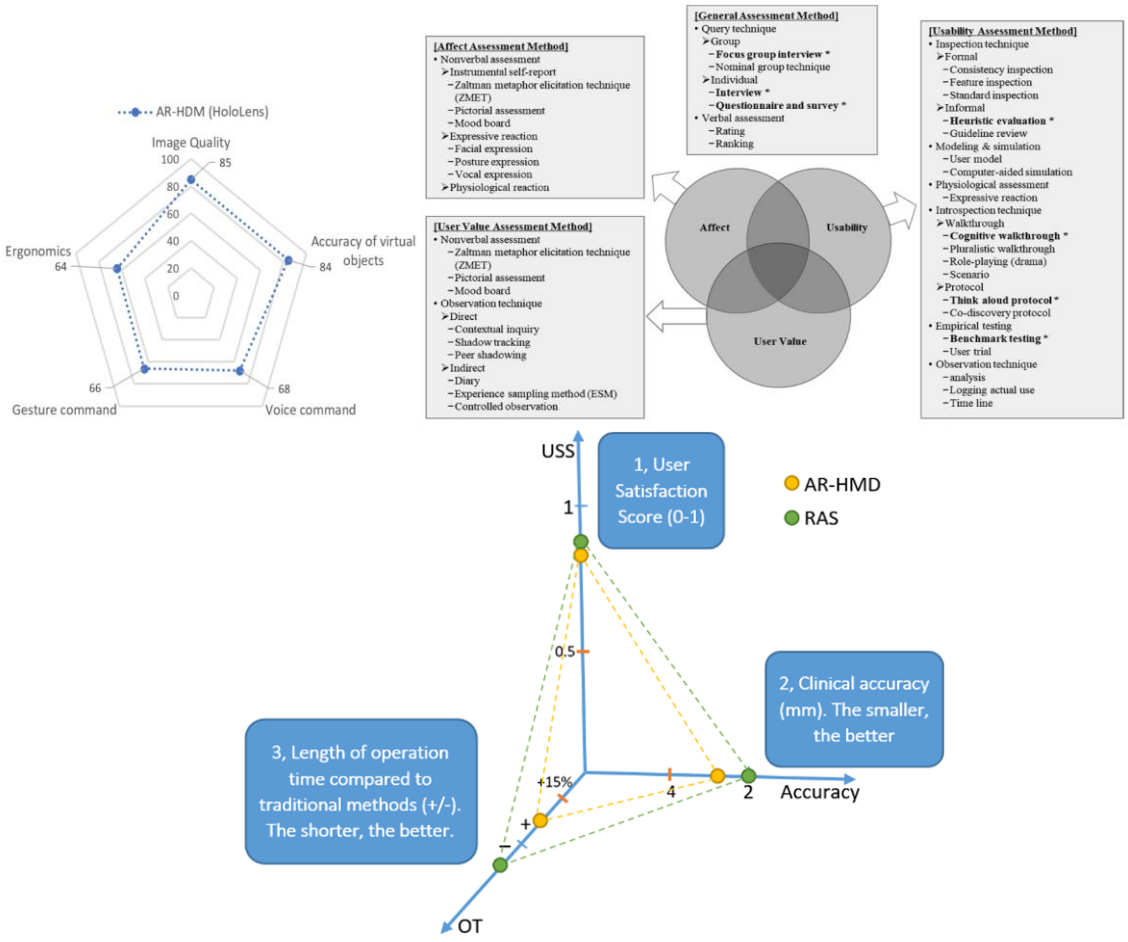
8.1 Integration of Extended Reality (XR) Technologies

Future technologies, such as Augmented/Virtual/Extended Reality (AR/VR/XR) will bring more complexities to the table, since the value of the actual development will be harder to measure [80] (Figure 8.1). The benefits of CAS/CIS systems and Augmented Reality Head-Mounted Displays (AR-HMD) in the field of surgery can be recognized in the cases presented in the recent literature. While the collected and reviewed accuracy data of AR–HMDs from the past three years did not show significant differences compared to RAS, and the AR-navigated procedure accuracy did not differ from phantom models, cadaver experiments and *in vivo* patients. As the more expensive FDA-approved robotic systems have been spreading, the cheaper, yet accurate alternative AR–HMD navigation systems seem to have reached their technological readiness level for wider adoption in living patient care in surgery.



8.1. Figure: The future of integrated OR concept with XR technologies [19].

The assessment of XR technologies integrated with surgical robots opens new, complex realities. Common frameworks are expected to be developed, since their contribution to the success of the complete digital medical device and system will be extremely complicated to quantify.



8.2. Figure: Proposing a novel framewrok for XR schoring and assessment is important. Examples of existing scoring for AR systems include. a) Based on the article by Dennler et al. [80]. b) Other mentioned methods based on the article by Bitkina et al. [81]. c) A proposed, integrated framewark by Moga et al. [19].

8.2 New domains of Surgical Data Science

Data in the clinical context is heterogeneous, based on multiple sources, not only intra-operative data, such as robot kinematics, laparoscopic video streams or device data, but also pre-processed clinical information and pre- and post-operative patient datasets have to be taken into account [17]. In SDS, such high-volume information stream has to be acquired and stored which involves several challenges, e.g., regarding interoperability or standards for storage [82]. Based on Big Data methods, new ML and AI applications can be developed, where possible deployment domains range from semi-automation of surgical tasks to context-aware surgical guidance.

Deep learning methods require large-scale annotated data sets for training, often a major bottleneck for applying such methods in robot-assisted surgery. Annotation is time-

consuming, and often highly qualified human experts are required. Current approaches try to overcome this by generating synthetic data sets, methods to speed up annotation, such as crowdsourcing or active learning, or self-supervised learning methods that do not require detailed annotations [17]. In addition, data sets have to be representative for the task to be solved, including possible anatomical and pathological variations, preferably from multiple centers and patient cohorts.

Apart from these particularly interesting areas, imminen future work incorporated the complete reprocessing of the surgical robotics dataset, together with the adjacent tables. This may lead us to a better understanding of major trends and future research.

9 ÖSSZEFOGLALÁS

A digitális orvosi eszközök valódi műszaki innovációt és új terápiás lehetőségeket hoztak az egészségügy számos területén. Kiváló példa, hogy megjelentek a sebészeti robotok, mint komplex hardver-szoftver rendszerek, amelyek jelentősen megváltoztathatják a hagyományos műtétek egész munkafolyamatát. A jelenlegi műtéti megközelítések valójában még csak továbbfejlesztést, asszisztenciát jelentenek a humán sebészek számára, ezért ezeket az eljárásokat jellemzően robot-asszisztált műtétekként kezelik.

Míg máig már több mint 300 sebészeti robot prototípust és műtéti rendszert fejlesztettek, ezek közül csak néhánynak sikerült kereskedelmi forgalomba kerülnie és szélesebb körben elterjednie, ami gazdasági sikert hozott.

Az egyik jelentős tényező, amely sok sebészeti robotrendszert megakadályozott abban, hogy időben, és mégis jó minőségű rendszerrel lépjen be a piacra, a minőségi és megfelelőségi szabványok összetettsége. Az orvostechnikai eszközök a legszigorúbban szabályozott területek közé tartozik a világon mindenhol, de különösen az Európai Unióban, miután 2021. májusában hatályba lépett az orvostechnikai eszközökről szóló Medical Device Regulation (MDR) rendelet. Ez jelentős kihívások elé állítja a gyártókat, különösen az alkalmazott mesterséges intelligencia és robotikai megoldásokat integráló fejlesztések esetében. Az MDR-követelmények között megtalálható a bizonyítandó klinikai előny vagy a non-inferior eljárás alátámasztása, amelyhez költséges klinikai vizsgálatokat, szisztematikus szakirodalmi áttekintést és egészségügyi technológiai értékelési eljárásokat kell lefolytatni.

A szakdolgozatom célja, hogy felmérje azokat a módszereket és eszközöket, amelyeken keresztül az USA Élelmiszer- és Gyógyszerügyi Hatósága (FDA) és a CE-jelölés típuskövetelményei szempontjából kezelhető az orvosi eszköztanúsítás összetett folyamata.

A dolgozat szisztematikusan bemutatja a jelenlegi sebészeti robot osztályokat és kiemelkedő rendszereket, valamint a különböző értékelési módszerek elemzését adja ezek számszerűsítésére és összehasonlítására. Egy párhuzamosan lefolytatott kutatásaink eredményeit integrálva megállapítható, hogy az EQ-5D jelentési standardjainak követése döntő fontosságú lenne a sebészrobotikai eredmények objektív értékeléséhez. Csak a szabványos riportolás garantálhatja az átláthatóságot, a vizsgálatok összehasonlíthatóságát és a különböző tanulmányok összesített metaanalízisét.

Amint az a szakirodalomból hiányzott, megvizsgáltam a lehetséges összefüggést a sebészeti robotrendszer fejlesztése és az engedélyeztetés, valamint a befolyt befektetési pénzek között. Míg szignifikáns összefüggések nem derültek ki, addig 32 kiemelkedő sebészeti robotfejlesztő és gyártó cég adatainak szisztematikus elemzése rávilágított a

befektetések időzítése, földrajzi elhelyezkedése és üzletnagysága közötti összefüggésekre.

Vitathatatlan, hogy most a sebészeti robotok térnyerésének lehetünk tanúi, ami révén biztonságosabb és hatékonyabb gépi asszisztensek fognak megjelenni rutinszerűen a műtőkben. A helyzetfelismerés javítása és a döntéshozatal támogatása mellett a mesterséges intelligencia a minőségbiztosításban, az eljárások értékelésében és értékelésében is jelentős szerepet fog játszani, szisztematikus adatokat bizonyítva az ember és a robot által elkövetett hibákról. Már most látjuk a sebészeti robotok alternatív koncepcióinak térnyerését, de az invazív orvostechnikai eszközökkel szemben támasztott szabályozási és biztonsági követelmények az utóbbi időben jelentősen megemelkedtek, ami további kutatásokat tesz szükségessé, elsősorban a rendszerek szoftver oldalán. A digitális orvosi eszközök jelenlegi és jövőbeli hatását nem lehet alábecsülni, ennek ellenére etikai és fenntarthatósági szempontok mentén kell keretek közé telrelnünk a vonatkozó fejlesztéseket.

10 SUMMARY

Digital medical devices brought great opportunities and new treatment options across healthcare domains. As a prime example, surgical robots appeared, as complex hardware-software systems able to significantly alter the workflow of traditional surgeries. Current approaches provide enhancements to the human surgeons, therefore these procedures are typically addressed as robot-assisted surgeries.

While there have already bene more than 300 prototypes and commercial systems built, only a handful of them managed to achieve commercialization and a wider adoption, yielding to a commercial success.

One of the anticipated hurdles that prevented many surgical robot systems from entering the market domains in time and yet with a high-quality system, is the complexity of the conformity and compliance requirements and standards. The medical device domain is among the most heavily regulated ones everywhere in the world, but especially in the European Union, after the Medical Device Regulation (MDR) came into effect in May 2021. This presents significant challenges to manufacturers, especially in the domain of applied Artificial Intelligence and robotics. Among the MDR requirements there can be found the need for proof of clinical benefit or non-inferiority, for which expensive trials, extensive literature review and health technology assessment procedures have to be initiated and conducted.

The aim of this thesis work is to assess the methods and means through which the complex process of device certification can be managed from the U.S. Food and Drug Administration (FDA) and the CE marking type requirements' point of view.

The thesis systematically introduces the current surgical robot classes and outstanding systems, and provides the analysis of the various assessment methods to quantify and benchmark these. Integrating the results of a parallel research conducted, it can be concluded that following the reporting standards of EQ-5D would be crucial for the objective evaluation of the results. Only standardized reporting can guarantee transparency, comparability across studies and the aggregate analysis (meta-analysis) of different studies.

As it has been missing from the prior literature, the possible correlation between surgical robot system development and clearance versus the collected investment money was investigated. While no statistically significant correlation was revealed, the systematic analysis of the data of 32 outstanding surgical robot developer and manufacturer companies highlighted connections between the timing, geography and deal size of the investments provided.

It is believed that we are now witnessing the rise of surgical robots, where safer and better assistants will make home in the Operating Room. Beside improving situation

awareness and supporting decision making, AI will also play a major role in quality assurance, in the evaluation and assessment of procedures, proving systematic data on human and robot made errors. We are already seeing the rise of alternative concepts of surgical robots, yet the regulatory and the safety requirements towards invasive medical devices have been raised significantly recently, making additional research necessary, primarily on the software side of the systems. The present and future impact of digital medical devices cannot be underestimated, yet we need to channel and frame it along ethical and sustainability considerations.

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13 LIST OF FIGURES

14 LIST OF ABBREVIATIONS

AI	Artificial Intelligence
AR-HMD	Augmented Reality-Head-Mounted Display
AR/VR/XR	Augmented/Virtual/Extended Reality
CAD	Computer-Aided Design
CAM	Computer-Aided Manufacturing
CAPEX	Capital Expenditure
CIS	Computer-Integrated Surgery
CE	Conformite Europeenne
CT	Computed Tomography
DMD	Digital Medical Device
DoF	Degree(s) of Freedom
EKIK	University Research and Innovation Center
ESG	Environmental, Social and Governance (aspects)
FDA	U.S. Food and Drug Administration
HIFU	Highly Focused Ultrasound
HTA	Health Technology Assessment
IEC	International Electrotechnical Commission
ISO	International Standards Organization
IP	Intellectual Property
IPO	Initial public offering
LoA	Level of Autonomy
M&A	Merger and acquisition
MDR	Medical Device Regulation
MEE	Medical Electrical Equipment
MES	Medical Electrical Systems
MIS	Minimally Invasive Surgery
ML	Machine Learning
MRI	Magnetic Resonance Imaging
OR	Operating Room
OU	Óbuda University
PMA	Pre-Market Approval
PRoM	Patient-Reported Outcome Measures
RA	Robot-Assisted (surgery)
RAMIS	Robot-Assisted Minimally Invasive Surgery
R&D	Research and Development
R&A	Robotics and Automation
QALY	Quality Adjusted Life Years
SDO	Standard Development Organization
SDG	Sustainable Development Goal
TRL	Technology Readiness Level
US	Ultrasound
WTP	Willingness to Pay

15 ANNEXES

Large tables not fitting the main text body.

Datasheets and raw materials are available: https://tinyurl.com/prrc-hat

TABLE I

A LIST OF MOST ADVANCED RAMIS SYSTEMS. ONLY TRL9+ ROBOTS ARE SHOWN, WHICH HAVE ALREADY ACHIEVED REGULATORY CLEARANCE IN AT LEAST ONE COUNTRY.

No	RAMIS System Name	Old name / legacy	Year	Producer/Manufacturer/Developer	HQ	Website	Capital invested in the dev. phase (public data)	Estimated # units sold
1	**da Vinci Surgical System Xi, X, 5**	da Vinci S, Si	FDA 2014 (FDA 2000)	Intuitive Surgical Inc.	Sunnyvale, USA	http://www.davincisurgery.com/	$250 m (1995-2004)	>9000
2	**Zeus (defunct 2003)**		FDA 2001	Computer Motion Inc.	Goleta, CA	https://en.wikipedia.org/wiki/ZEUS_robotic_surgical_system	n/a	<50
3	**Senhance Surgical Robotic System**	ALF-X	FDA 2017 (CE 2011)	Asensus Surgical Inc. (before: TransEnterix Surgical Inc., Sofar S.p.A.)	Morrisville, NC	https://www.senhance.com/	$263 m (2013-)	<100
4	**X-Surgical**	Surgenius	(CE 2012)	X-Surgical (prior: Surgica Robotica S.p.A)	Cambridge, MA (prior: Verona, IT)	http://surgrob.blogspot.com/2019/08/x-surgical-presents-its-first-prototype.html	n/a	0
5	**Revo-i,**	Eterne	Korean MFDS 2017	Meere Robot	Soeul, KR	http://revosurgical.com/	$38.8 m (2011-)	<20
6	**Versius**		CE 2019	CMR Surgical (before: Cambrdige Medical Robotics)	Cambridge, UK	http://www.cmedrobotics.com/product/	$ 947.7 m (2016-)	>200
7	**avatera**		CE 2019	avateramedical	Jena, DE	https://www.avatera.eu/start/	$ 203 m (2011-)	<10
8	**hinotori**		CE 2020 (JP 2019)	Medicaroid, Kawasaki Heavy	Kobe, JP	https://www.medicaroid.com/en/product/hinotori/	n/a	<20
9	**Dexter**		CE 2020	DistalMotion SA	Lousanne, CH	http://surgrob.blogspot.com/2018/06/distalmotion-democratizing-robotic.html	$ 17m (2011 -)	<5
10	**Symani Surgical System**		CE 2020	MMI microsurgery platform	Calci, IT	https://www.mmimicro.com/	$ 20m (2015 -)	<5
11	**Toumai Endoscopic Robot**		CFDA (NMPA) 2021	MicroPort Medbot	Shanghai, CN	http://surgeniusinstruments.com/aboutus.html	$ 512 m (2014-)	0
12	**Mantra**		India temporary, 2021	SS Innovations (China: Robosurg Pte. Ltd.; Singapore: SSI Group Company)	Cambridge, MA, Hangzou	http://www.ssinnovations.org/	n/a	<10
13	**Hugo RAS System**	Einstein	CE 2021	Medtronic plc	Dublin, IE	https://www.medtronic.com/covidien/en-us/robotic-assisted-surgery/hugo-ras-system.html	n/a	0
14	**Bitrack**		CE 2022*	Rob Surgical System	Barcelona, ES	http://www.robsurgical.com/bitrack.html	$ 10 m (2012-)	0
15	**Micro Hand S**	Micro Hand A	in progress	Nankai Uni. and Tianjin Medical Uni. & General Hospital	Tianjin, CN	http://www.tju.edu.cn/english/info/1011/4091.htm	n/a	0

TABLE II

A COMPREHENSIVE LIST OF RECENT IMAGE-GUIDED INTERVENTIONAL SYSTEMS. ONLY TRL7 AND MORE ADVANCED RESEARCH PROTOTYPES ARE SHOWN. STATUS INDICATORS: R – RESEARCH, P – PRECLINICAL, C – COMMERCIAL OR D – DEFUNCT. TKA: TOTAL KNEE ARTHROPLASTY, MRGFUS: MRI-GUIDED FOCUSED ULTRASOUND

#	System Name	Old name	Status	Manufacturer/Developer	HQ	Type	Target procedures	Reg. approval	Website	capital invested
1	**AQRate**		D	KBmedical, acquired by Globus	Ecublens, Switzerland			CE	http://www.kbmedical.com	
2	**AquaBeam**		C	PROCEPT BioRobotics	Redwood, CA	Prostate ablation	Prostate ablation	FDA, CE	http://www.procept-biorobotics.com/technology.php	$173m; 2020: $77m
3	**ARTAS iX**	ARTAS v3	C	Restoration Robotics Inc.	San Jose, USA	Aut. folliculi harvest and implantation	hair restoration	FDA, CE	http://www.restorationrobotics.com/	$118 m as of 2015; In 2016 $4.82 m equity funding , Restoriation
4	**Arthrobot**		R	Jointech (Jianjia Robots)	Beijing? China	Arthroplasty				Series B $14.72m, in 2020
5	**ASRS**	AVRA Surgical System, LISA	P	AVRA Surgical Robotics Inc. LG Mechatronic	New York, USA	IG robot with needle	Skin resurfacing		http://www.avrasurgicalrobotics.com/	
6	**Automated Needle Targeting (ANT)**		R	NDR Medical Technology Pte / MicroPort	Singapore	Needle guidance			https://www.biospectrumasia.com/news/27/16329/singapores-surgical-robotic-firm-ndr-medical-closes-sgd8m-in-series-a-funding-round.html	2020: $5.75m
7	**BEAR: Brescia Endoscope Assist**		R	University of Brescia	IT	IGS	transnasal skull base surgery			
8	**BioBot**	iSR'obot Mona Lisa	C	Biobot Surgical PTE Ltd.	Singapore	IGS	Prostate biopsy	U.S. FDA 510(k) (2022)	http://www.biobotsurgical.com/product/NonCate/iSRobot-Mona-Lisa	2011: $4m
9	**CASPAR**		D	OrthoMaquet Rastatt	Rastatt, Germany					
10	**CORI Surgical System**		C	Smith + Nephew	London	IGS hand held	UKA and TKA		http://surgrob.blogspot.com/2020/07/cori-surgical-system-from-smithnephew.html	
11	**CUVIS-joint**		P	Curexo		IGS	total knee arthroplasty		http://www.curexo.com/english/medical/sub01p03.php?PHPSESSID=f9d09f37ef54517e5efd5dabef7fe6e8	
12	**CUVIS-spine**		P	Curexo		IGS	spine pedicle screw		http://www.curexo.com/english/medical/sub05.php?PHPSESSID=0779c9f63527a2a9828f59d8e6755c50	
13	**Cyber Surgery**		R	Cyber Surgery is a spin-off of Egile Corporation XXI.		IGS	spine surgery		https://cyber-surgery.com/	
14	**DePuy Synthes**	Orthotaxy	C	J&J		IGS	orthopaedic, TKA		https://www.jnjmedtech.com/en-US/companies/depuy-synthes	
15	**eCential Robotics**		R	Ecential Robotics SAS	Paris, FR	IGS	Spine		https://www.ecential-robotics.com/en/products	In 2021.02: $120m series B
16	**EPICA**		R	EPICA International		CT-guided			https://www.epicainternational.com/businesses/medical-robotics	
17	**Epione**		R	Quantum Surgical	Montpellier, FR	IG liver surgery	Liver biopsy	FDA 510(k), 2022	https://objectif-languedoc-roussillon.latribune.fr/innovation/innovation-medicale/2018-04-10/comment-quantum-surgical-innove-sur-le-traitement-du-cancer-du-foie-774841.html	$50m in series A, June 2018
18	**ExAblate 2000**		C	Insightech Ltd.	Tirat Carmel, IL	MRgFUS		FDA	https://insightec.com/exablate-body/	$632.9M in 10 series since 2010
19	**Excelsius GPS**		C	Globus Medical			IG pedicle screw placement			
20	**Fraunhofer Needle placement robot**		R	Fraunhofer IPA	Stuttgart, DE	KUKA iiwa and CT	needle placement		http://surgrob.blogspot.hu/2016/11/fraunhofer-ipas-new-needle-positioning.html	
21	**HEARO**	ARTORG IGS robot	P	CAScination AG, together with MED-EL GmbH, University of Bern	Switzerland	IG drilling	Cochlear implant		http://surgrob.blogspot.hu/2017/03/artorg-image-guided-robot-for-cochlear.html	
22	**HistoSonic**		P	HistoSonic	Ann Arbor, Mich	IGS	non invasive heat therapy/HIFU		https://histosonics.com/	$54m in 2019 J&J partnership
23	**HKU robot**		R	University of Hong Kong	Hong Kong	MR safe neuosurgery	stereotaxis		https://www.surgicalproductsmag.com/article/2018/06/worlds-first-intra-operative-mri-guided-robot-bilateral-stereotactic-neurosurgery	

24	**HURWA**		R	Beijing Hurwr Medical Technology	Beijing, CN	IGS	knee surgery		http://www.beijingetown.com.cn/2022-03/01/c_720866.htm	
25	**IotaMotion**		R		Midwestern US	IGS	robotic cochlear implant system		IotaMotion	$6.7 m+1.65 NIH grant
26	**Keranova**		R	Keranova	Lyon, FR	IGS	photoemulsification of cataractous lenses		https://www.keranova.fr	
27	**Kymero**		R	Koh Young Technology	Korea	IGS	Neuro		https://www.bioworld.com/articles/455846-koh-young-aims-for-kymeros-global-expansion-after-netting-first-sale?v=preview	$17m
28	**Machnet**		R	Machnet Medical Robotics	Twente	IGS	IG neural			
29	**MAXIO**	PIGA	D	Perfint Healthcare Pvt. Ltd.	Tamil Nadu Chennai, India			FDA, CE	http://www.perfinthealthcare.com/MaxioOverview.asp	$33 m
30	**Mazor Renaissance**	SpineAssist	C	Mazor Robotics Ltd / acq by Medtronic	Orlando, Florida, USA / Dublin, IE				http://mazorrobotics.com/renaissance/	$72m investment from Medtronic 2016-2018; $1.6bn buy option
31	**Mazor X / Mazor X Stelath Edition**		C	Medtronic		othopaedic IGS robot	TKA		https://www.medtronic.com/us-en/healthcare-professionals/products/spinal-orthopaedic/spine-robotics/mazor-x-stealth-edition.html	
32	**Micromate**	B-Rob, iSYS	C	iSYS Medizintechnik GmbH / Partial acq by Medtronic	Kitzbühel, Austria			FDA, CE	http://www.isys.co.at/	
33	**MIRIAM needle positioning robot**		R	DEMCON / U Twente		IG	Needle placement		https://www.demcon.nl/en/showcase/miriam/	
34	**Monogram**		R	Monogram Orthopaedics		IGS	Joint replacement		https://www.kuka.com/en-hu/industries/loesungsdatenbank/2021/02/monogram-orthopaedics	
35	**NaoTrac**		P	Brain Navi Biotechnology	Taiwan	IGS	neurosurgery	CE (2021)	https://jerrychen0.wixsite.com/brainnavi	
36	**NavioPFS**	HipNav	C	Smith & Nephew	Plymouth, Minnesota, USA				http://bluebelttech.com/products/navio/partial-knee-replacement/	Acquired from Blue Belt Technologies Inc. in 2015 for $275m
37	**Neuralink**		**R**	**Neuralink**		Electroide implant			https://gizmodo.com/elon-musks-neuralink-says-its-created-brain-reading-thr-1836435602	$158m in 2017
38	**neuromate**	NeuroMate	C	Renishaw plc	Gloucestershire, United Kingdom				http://www.renishaw.com/en/neuromate-stereotactic-robot--10712	
39	**Neurostar TMS Therapy System**		D	Neurostar	**Tübingen, Germany**				https://neurostar.com/what-is-neurostar-advanced-therapy	
40	**Niobe**		C	Stereotaxis Inc.	**St. Louis, Missouri, USA**				http://www.stereotaxis.com/products/niobe/	$15m in 2020
41	**Omnibotics**	A.R.T.	C	OMNI Life Science Inc.	Massachusetts, USA	Surgical navigation/assistance			https://www.coringroup.com/healthcare-professionals/solutions/omnibotics/	
42	**OncoRobot**		R	Russian State Scientific Center for Robotics and Technical Cybernetics	RU	IG needle placement	Prostate brachy			
43	**Phecda**	Tianji	P	Beijing Tinavi	Beijing, China	IG surgery	spine surgery, pelvic and spinal fracture	CNDA	http://surgrob.blogspot.hu/2017/01/the-rise-of-medical-robotics-in-china.html	
44	**Pulse**		C	Nuvasive		IGS	Spine		https://www.nuvasive.com/news/nuvasive-launches-pulse-the-first-integrated-technology-platform-to-enable-better-spine-surgery/	
45	**RAFS**		R	MatOrtho, Bristol University	Bristol, UK	IG orthopaedic robot	fracture reduction		surgrob.blogspot.com/2018/07/uwe-bristols-rafs-fracture-reduction.html	
46	**Remebot**		C			IG surgery	frameless neursurgery	CNDA, CE	www.remebot.com.cn/	Early: 19.8m 2020.12: $66m in Series D

47	**RIO System**	MAKO	C	Stryker Inc. (formerly MAKO Surgical)	Florida, USA				http://www.makosurgical.com/	Acquired for $1.65bn
48	**ROBOSCULPT**		R	Medical Robotic Technologies BV	Eindhoven	IG drilling			https://www.medica-tradefair.com/vis/v1/en/exhibitors/medcom2017.2553825	
49	**Ronna**		C						http://www.ronna-eu.fsb.hr/index.php?lang=en	
50	**ROSA BRAIN**		C	Zimmer Biomed (Formerly Medtech sarl)	Montpellier, France		Spine, also for TKA		http://medtech.fr/en/rosa1	Acquired for $132m
51	**ROSA SPINE**		C	Medtech /Acquired by Zimmer Biomed 2016	Montpellier, France				http://medtech.fr/en/rosa1	Acquired for $132m
52	**Skywalker**		R	MicroPort	Shanghai	Ortopedic robot				
53	**Sonalleve**		C	Philips Healthcare	Best, NL	MRgFUS	HIFU treatment of uterine fibroids and bone metastases		https://www.philips.ie/healthcare/product/HC781360/sonalleve-mrhifu-therapy-platform	
54	**Stanmore Sculptor**	Acrobot	D	Stanmore Implants Ltd. (acquired by MAKO)	Elstree, United Kingdom				http://www.stanmoreimplants.com/	
55	**SurgiBot**		D	TransEnterix Surgical Inc.	Morrisville, NC		General MIS		http://www.transenterix.com/technology/surgibot/	$263m as of Aug 2017
56	**Tamar Robotics**		R	Tamar Robotics		MIS neurosurgery	brain mass removal		https://www.tamarrobotics.com	
57	**THINK Surgical**	ROBODOC	C	Curexo Technology Corp (formerly ISS)	Fremont, California, USA				http://thinksurgical.com/	2019.03: $134m raised
58	**Yomi**		C	Neocis	FL	IG drilling	dental implants		http://surgrob.blogspot.hu/2017/03/yomi-first-robot-for-dental-implant.html	$48 m + $72m as of 2020.10.
			(Research/Preclinical/Commercial/Defunct)							

TABLE III

RAW DATA FOR TABLE III.

No	System Name	Company name	link	Region	DEV TIME (months)	Complete amount (over total existance, m$)
14	Micromate	Interventional systems, iSYS Medizintechnik GmbH / Partial acq by Medtronic		EU	120	3
90	AQRate	KBMedical		EU	72	9.11
25	THINK Surgical	Think Surgical		USA	72	13.5
50	BioBot	Biobot Surgical PTE Ltd.		Asia	107	23.9
13	Invendoscope	invendo medical		EU	98	28
17	MAXIO, ROBIO EX	Perfint Healthcare Pvt. Ltd.		Asia	90	33.6
48	FLEX	Medrobotics		USA	105	59.2
7	CyberKnife	Accuray		USA	120	70
23	Renaissance	Mazor		IZ	36	91
255	Maestro	Moon Surgical		EU	51	94
30	Sensei X2	Hansen		USA	120	124.5
81	MIRA MIS robot	Virtual Incision		USA	212	153.4
3	ARTAS	Restoration Robotics	https://www.crunchbase.com/organization/restoration-robotics/company_financials	USA	129	154.4
43	Alf-X (Luna)	Asensus Surgical Inc.		USA	54	212.9
8	da Vinci Surgical System	Intuitive		USA	36	235
6	Corindus	Siemens Healthineers Endovascular Robotics	https://www.crunchbase.com/organization/siemens-healthcare	USA	111	240.9
160	Dexter	Distal Motion		EU	106	243.25
127	Avatera	Avatera		EU	101	272
58	Enos	Titan Medical		USA	192	279.9
213	Edge	Edge medical robotics		Asia	69	310.81
106	Monarch	Auris Surgical Robotics		USA	114	739.2
128	Versius	CMR Surgical		EU	57	363.3
18	NavioPFS	Smith & Nephew		USA	90	
19	NeuroMate	Renishaw		EU	180	
24	RIO System	MAKO		USA	48	
26	ROSA BRAIN	MedTech		EU	120	
27	ROSA ONE SPINE	Zimmer BIomet		USA	74	
29	ROSA Knee, Hip	Zimmer BIomet		USA	88	
31	SOLOASSIST II	Aktor		EU	156	

THE END