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Original paper

Patient-tailored brachytherapy applicator development in compliance with the EU medical device regulation

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ABSTRACT

Background and purpose: Clinical introduction of in-house developed medical devices in Europe requires conformity to the Medical Device Regulation (MDR) 2017/745 Article 5(5). Published experience on regulatory aspects of these devices is limited. This work describes our in-house development and verifications of the 3D printed patient-tailored ARCHITECT brachytherapy applicator and accompanying software, prepared to support clinical investigation and in-house use.
Materials and methods: Article 5(5) mandates an 'appropriate' quality management system (QMS) and exempts in-house medical devices from all MDR requirements except general safety and performance requirements (GSPRs). An institutional QMS was available, comprising documented procedures and fill-in templates for all project phases to compile technical documentation. In the first phase, the QMS requires a market analysis to justify the in-house exemption. In the design phase a prototype is developed, to be iteratively improved during manufacturing and verification phases, based on risk evaluations, verification tests, and processing constraints. Documentation is lastly compiled to support clinical investigations and routine use of the device.
Results: After confirming that no suitable marketed device was available, risk-based design and manufacturing approaches were used to safeguard in-house development. Verifications of material, manufacturing, mechanical safety, cleaning and sterilisation, use and workflow, and compatibility with procedures showed compliance with GSPRs. Simulated dosimetric benefits were observed compared to marketed devices.
Conclusion: The ARCHITECT applicator was developed in a systematic process, resulting in documented workflows and verification steps. Our approach provides a practical framework for MDR-compliant introduction of in-house equipment and can inform future best practice guidelines.

1. Introduction

The European Union Medical Device Regulation (EU MDR) 2017/745 came into full application on May 26, 2021 [1]. Compared with its predecessors, it imposes more stringent requirements for placing medical devices on the market and/or using them in clinical practice [2,3]. Among others, the MDR revised its scope, updated the risk classification, reformed safety and performance requirements, stipulated clinical evaluations and data collation, e.g., through post-market surveillance (PMS), and redefined the role of notified bodies [4–7]. To aid implementation and application of the MDR, manufacturers or notified bodies can use guidance documents from the Medical Devices Coordination Group (MDCG) [8], and harmonised standards [9]. Additionally, manufacturers may need to account for a range of other regulations, standards, and common specifications. Relevant EU legislation may include device-specific rules such as the In Vitro Diagnostic Regulation (IVDR) 2017/746 [10], the Directive 2013/59/Euratom [11], and the Artificial Intelligence (AI) Act 2024/1689 [12–14], as well as horizontal legislation such as the Product Liability Directive 2024/2853 [15], or the General Data Protection Regulation (GDPR) 2016/679 [16]. Other

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national regulations can additionally apply within the EU member states, e.g., for performing clinical investigations. Furthermore, relevant standards, such as those issued by the International Organization for Standardisation (ISO), International Electrotechnical Commission (IEC), or American Society for Testing and Materials (ASTM) need to be considered. And lastly, (inter)national commission recommendations may be applicable, such as those for medical physics applications by the International Commission on Radiation Units and Measurements (ICRU), International Commission on Radiological Protection (ICRP), or American Association of Physicist in Medicine (AAPM) task groups (TG). The changes in the EU medical device legislation may be regarded as an effort to prevent future safety issues and reduce the frequency of alerts and recalls, as experienced under the previous directive [17]. Moreover, it encourages 'more' systematic and rigorous approaches to develop, evaluate, manage and monitor devices [18,19]. However, the MDR increases the burden for manufacturers and authorities, and is argued to preserve a system that lacks clarity, uniformity and centralised accountability [14,20]. This may slow down, and even hamper, both new device development and market entry [21], as well as continuation and availability of existing medical devices [22].

The MDR also regulates 'in-house' development (i.e., by health institutions) of medical devices, including medical device software (MDSW), which is commonly performed when commercially available devices fail to meet specific clinical needs. Medical physicists can for example be involved in developing tools for diagnosis, imaging and delineation, treatment planning, dose calculation, and (customised) irradiation devices. Devices that are 'custom-made' (i.e., prescribed to an individual patient) and possibly manufactured in-house are subject to specific requirements distinct from the standard MDR conformity assessment procedures, as discussed in several papers [23–25]. In-house developed or modified medical devices –that are not custom-made– are exempt from the MDR requirements except for general safety and performance requirements (GSPRs, Annex I, MDR), provided that the conditions specified in Article 5(5) are met [26]. This includes no transfer to another legal entity, justification that the target patients' needs/performance cannot be met by a commercially available medical device, and manufacturing (on a non-industrial scale) and use under 'appropriate' quality management systems (QMS) [1,27]. Although the MDR requirements not covered in the Article 5(5) exemption do not formally apply for in-house development, the Regulation is often used as a reference for good practices, such as technical documentation, clinical investigations, and risk classification. Several works have attempted to provide guidance on regulatory compliance for in-house developed medical devices [13,14,26,28], but these lack practical examples. Case examples or studies of in-house developed or custom-made devices with clear procedural descriptions are scarce [24,29–31]. In the context of medical physics applications, MDR compliance of in-house developed MDSW has been described [32,33], but with limited procedural details. Some studies have documented efforts on MDR-related procedural steps, such as risk analysis [34], QMS [35], or performance/safety evaluations of 3D printed medical devices [36–38]. As such, there remains a need for detailed, practice-oriented case studies that document regulatory processes for in-house medical devices.

In this work, we describe our systematic approach to the MDR-compliant in-house development and evaluation of a novel 3D printed patient-tailored applicator for cervical cancer brachytherapy (BT; internal irradiation), called the ARCHITECT applicator, with accompanying software. The ARCHITECT applicator's outer geometry and (curved) needle channels are adapted to the patient's anatomy. By customising needle placement, this applicator is expected to improve brachytherapy treatment plan quality. Initially, applicator generation was performed manually [39], which is currently automated with dedicated software [40]. Given the use of standardised operations and geometry to design the applicator, we consider this to be a 'patient-matched' medical device (i.e., custom-made procedures do not apply) [41]. As the software and the applicator cannot achieve their intended purposes independently, they are considered together as a single medical device [42]. To enable routine clinical in-house use in accordance with Article 5(5), sufficiently detailed documentation demonstrating device compliance with the GSPRs, supported by verifications and clinical investigation, is required. In the Netherlands, documentation known as an Investigational Medical Device Dossier (IMDD) is currently also required to use medical devices without CE-marking in clinical investigations (following Article 82, MDR) [43]. Similar documentation is mandated in other EU member states. This paper describes our work following the MDR framework, including Article 5(5), to prepare the documentation required for clinical investigation and anticipated routine clinical use of the in-house developed ARCHITECT applicator. It may serve as a practical example for compiling MDR-compliant technical documentation for in-house developed medical devices.

2. Materials and methods

2.1. General overview

At our university hospital, the Erasmus Medical Centre (Rotterdam, the Netherlands), a structured workflow is used for in-house developed medical devices consisting of five phases: (1) Preliminary investigation and justification; (2) Design; (3) Manufacturing and verification; (4) Validation; and (5) Post-investigational use and conformity assessment [31]. Risk management is an integral part of phases 2–5 and is iteratively updated. Upon completion of the first three workflow phases, the IMDD can be compiled which is analogous –with exception of post-investigational use aspects– to the technical documentation in Annex II of the MDR. In this article, we specifically focus on these phases required to initiate clinical investigation (Fig. 1). Workflows and templates were made available in Microsoft Word and Excel, and were collected on a web-based platform created by our Medtech Innovation Support Office (MISO). These documents were structured as fill-in templates with a document history and approval frontpage, with sections referring to annexes for detailed information. After each phase, completed documents were sent for review to MISO and other competence centres within the hospital.

2.2. Preliminary investigation and justification

To justify in-house development, it must be demonstrated that clinical needs cannot be sufficiently met by (off-label use of) commercially available medical devices, or modification by the manufacturer of these devices. Therefore, this phase consisted of (Fig. 1, Step 1): (a) specification of intended purpose, (b) determination of the programme of requirements, and (c) market analysis and justification. First, it was determined whether the applicator and software qualify as a medical device (Article 2, MDR), and thus whether the MDR applies. Intended purpose specification included detailing of the intended patient population, intended user, type of use (e.g., frequency, duration, and contact with patient or user considering EN ISO 10993–1:2018 [44], and sterility), and claims (intended clinical benefits and precautions). Definitions were adopted from IEC 62366–1:2015 [45]. In accordance with the latter, a process tree was constructed to outline user interactions with the applicator and software [46,47]. This helped compiling a programme of requirements, categorised in essential requirements (i.e., to meet the intended purpose), and requirements related to other phases in the process tree. For the market analyses, product brochures of vendors were studied and the commercial applicators were evaluated with respect to the essential requirements. A rationale for in-house applicator development was subsequently written.

2.3. Design

The in-house developed device has to meet the GSPRs in Annex I of the MDR. GSPRs include general requirements (e.g., on risk

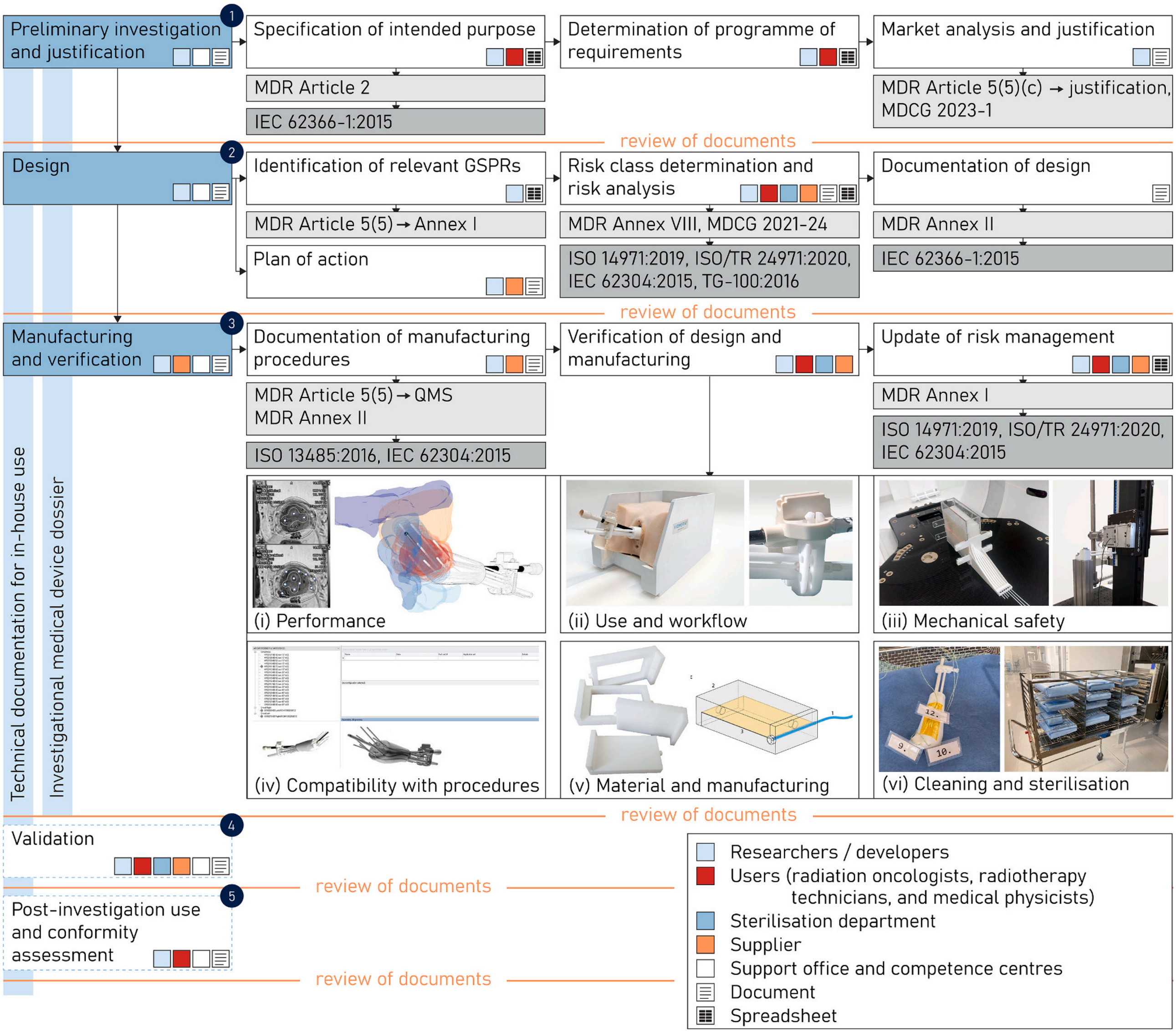


Fig. 1. Scheme showing major steps in the regulatory workflow of the in-house developed ARCHITECT applicator and accompanying software. In this article, the scope is limited to the first three stages to provide technical documentation for clinical investigation (the investigational medical device dossier). Light grey blocks indicate the relevant MDR Annexes and Articles, and dark grey blocks indicate relevant standards and guidelines used for our application. Document and spreadsheet icons indicate the type of fill-in template provided for our in-house QMS, and coloured squares the relevant stakeholders. Figure adapted from van Kempen et al. [31].

management and achieving performance in accordance with the intended purpose), design and manufacturing, and information to be supplied. In this phase, the following steps were performed (Fig. 1, Step 2): (a) identification of relevant GSPRs, (b) risk class determination and risk analysis, and (c) creation and documentation of design. Documentation provided in this phase was aligned with Annex II of the MDR, Sections 1 to 5. A checklist document for GSPRs was supplied and filled in. The risk class of the combined applicator and MDSW –which, for in-house devices, serves only as a reference for risk [26]– was determined using Annex VIII of the MDR and MDCG 2021-24 [48], and the MDSW safety class was assigned according to IEC 62304:2015 [49]. Risk management was performed in accordance with EN ISO 14971:2019 and included stakeholder meetings [50]. The process tree and methods in guidance document ISO/TR 24971:2020 were used for hazard identification [51]. Risk management included determination of risk levels, compilation of the risk matrix (determining probability and severity of potential harms), specification of risk control measures, and justification whether benefits outweigh the (residual) risks. This process enabled direct coupling between procedural steps, requirements, risk control measures, and evaluations, as also required per IEC 62304:2015 for the MDSW [49]. The operating principles, defined as methods to accomplish the intended use and corresponding mechanisms [45], were specified based on the requirements, risk analysis, and functional analysis. The MDSW was decomposed into modules, for which a series of input–output relationships and corresponding integration tests were devised. Device design iterations were created and modifications were tracked using flowcharts and version control software. Lastly, plans were created for subsequent phases: manufacturing and verification, and validation. Here, verification refers to design criteria checks, and validation refers to intended use and (pre)clinical performance checks [52].

2.4. *Manufacturing and verification*

The manufacturing and verification phase included (Fig. 1, Step 3): (a) documentation of manufacturing procedures, (b) verification of design and manufacturing, and (c) update of risk management. In-house development requires an ‘appropriate’ QMS for manufacturing. Therefore, a company that is certified to EN ISO 13485:2016 within the scope of 3D printing of medical devices was selected as supplier [52]. Manufacturing process flowcharts, quality assurance documentation, and material characterisation reports were obtained from the supplier. Documents related to cleaning, disinfection and sterilisation were acquired from the in-house Central Sterilisation Department. Quality assurance protocols were developed to safeguard manufacturing of each 3D printed applicator. For the MDSW, development was fully performed in-house and quality management was informed by IEC 62304:2015 [49]. Core MDSW modules were implemented, and an issue tracking system was adopted for development activities, maintenance, or user-requested modifications. Quality assurance of the MDSW was supported through automated verification tests per module, as well as requesting the user to review and confirm intermediate outputs. Several verifications were performed to demonstrate compliance of the medical device with the requirements and specifications. These include verifications of: (i) performance; (ii) use and workflow; (iii) mechanical safety; (iv) compatibility with procedures; (v) material and manufacturing; and (vi) cleaning and sterilisation (Supplementary Table S.1). These verifications were used to iteratively improve the design, and to adjust evaluations of residual risks in the risk management file. Materials were assembled in preparation for the validation phase including the clinical investigation plan, product information, and supporting materials.

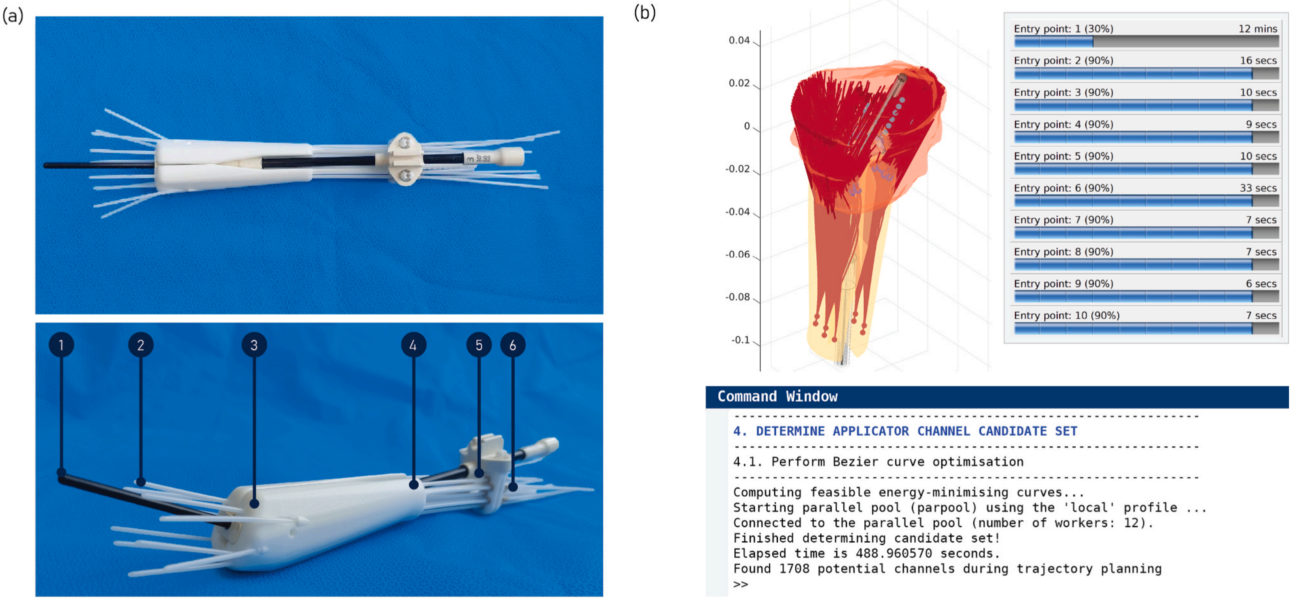
3. Results

3.1. General overview

Development and documentation of the applicator and software were performed in line with requirements for clinical investigation. During this process, feedback was obtained from relevant stakeholders, including medical physicists, radiation oncologists, radiotherapy technicians, MISO, the supplier of the 3D printed applicators, the Central Sterilisation Department, and a patient advocacy group. The patient-tailored ARCHITECT applicator and the MDSW are shown side-by-side in Fig. 2. The applicator consists of two 3D printed halves that are customised to the individual's anatomy and connect to a commercially available intrauterine tandem. The applicator body contains curved channels to guide (conventional) plastic needles for interstitial (IS) and intracavitary (IC) positioning of sources. The MDSW automatically generates the device embodiment based on medical image-derived plan data from a previous application, typically performed one week earlier. For the first application, a conventional BT applicator with packing is used; for each subsequent application, a patient-tailored applicator is generated. Details on the software implementation have been previously described [40].

3.2. Preliminary investigation and justification

The intended purpose was defined as use in patients with locally advanced cervical cancer (FIGO stages IB-IV), including those with parametrial, vaginal or nodal involvement, as part of an image-guided adaptive BT workflow [53], aiming to improve dosimetry over commercially available applicators (Table S.2 in supplementary material). The ARCHITECT applicator and software are intended to be used by health care professionals, including radiation oncologists, medical physicists and technicians trained in BT. As it is tailored to each application, the applicator is intended for single use. It is sterilised by the hospital prior to use and will be in contact with the (vaginal) mucosa and cervix (compromised surfaces) (see EN ISO 10993-1:2018 [44]). In the process tree (Table S.4 in supplementary material), the device's lifecycle (manufacturing, use, installation and maintenance, and disposal) was detailed. A programme of requirements for the applicator was categorised into two main groups: essential requirements –relating to source positioning, applicator placement, and imaging compatibility– and requirements regarding the medical device's lifecycle. Essential are the ability to position sources according to the patient anatomy, including IS needle angles of at least up to 20° relative to the tandem to reach parametria [54–56], and caudal source placement to cover vaginal extensions. Market analysis and consultation with one of the vendors indicated that none of the commercially available applicators fulfilled all essential requirements, and existing devices could not be modified to achieve the necessary patient-specificity. In addition, no existing MDSW could be adapted to (automatically) generate the applicator, justifying in-house development of the medical device including MDSW.



```
Entry point: 1 (30%)        12 mins
Entry point: 2 (90%)        16 secs
Entry point: 3 (90%)        10 secs
Entry point: 4 (90%)         9 secs
Entry point: 5 (90%)        10 secs
Entry point: 6 (90%)        33 secs
Entry point: 7 (90%)         7 secs
Entry point: 8 (90%)         7 secs
Entry point: 9 (90%)         6 secs
Entry point: 10 (90%)        7 secs
```

```
-------------------------------------------------------------
4. DETERMINE APPLICATOR CHANNEL CANDIDATE SET
-------------------------------------------------------------
4.1. Perform Bezier curve optimisation
-------------------------------------------------------------
Computing feasible energy-minimising curves...
Starting parallel pool (parpool) using the 'local' profile ...
Connected to the parallel pool (number of workers: 12).
Finished determining candidate set!
Elapsed time is 488.960570 seconds.
Found 1708 potential channels during trajectory planning
>>
```

Fig. 2. Illustrations of the 3D printed patient-tailored ARCHITECT applicator and the accompanying planning software. (a) Panel showing views of applicator assembly, containing: (1) Geneva intrauterine tandem (Elekta AB), (2) ProGuide interstitial needle (Elekta AB), (3) patient-tailored applicator body, (4) entry region, (5) needle fixation template, and (6) needle lock insert (Elekta AB). (b) Collection of panels in the needle channel planning phase of the software, which is implemented in MATLAB (R2021b). A large set of candidate needle trajectories is shown, planned within the applicator body and target region.

3.3. *Medical device design*

Relevant GSPRs and appropriate verification methods and procedures (for example ISO standards) were first identified in this phase (example shown in Table S.3 in supplementary material). The applicator and software were classified as a class IIa device per Rules 5 and 11 (Ch. III, Annex VIII), and implementing Rule 3.3 (Ch. II, Annex VIII). The MDSW was classified as safety class A in accordance with IEC 62304:2015, as failure of the software –after implementation of risk control measures– does not result in unacceptable risks. In both cases, it was considered that: (i) a conventional applicator can be used if a significant risk is detected at any stage, with the MDSW only employed during the preparatory phase, (ii) treatment planning and irradiation are prepared and performed with CE marked devices (needles, transfer tubes, afterloader, treatment planning software, etc.), and (iii) sources are never in direct contact with the applicator. For hazard identification in the risk analysis, the safety requirements, process tree, and Annex A of ISO/TR 24971:2020 were used. Risk levels were defined in a first stakeholder meeting, and an inventory of the largest risks per procedural step in the process tree was made. For risk level determination, definitions in TG-100:2016 were considered [47], but probability levels were adjusted based on evaluations of the application. A total of 113 risks were subsequently identified and assigned probability and severity scores (example shown in Table S.5 in supplementary material). Risk control measures were devised primarily related to design characteristics. In a second stakeholder meeting, major residual risks were discussed, and risk scores were updated.

Based on the risk and functional analysis, operating principles and design characteristics related to safety were refined. Features of conventional applicators were preserved to support familiarity and reduce risks, such as applicator assembly (same connector types), needle insertion and locking mechanism (same accessories and procedures), immobilisation (same procedure), and reconstruction (same library-based workflow). Design parameters, including the diameter at the introitus and apex, along with the decision for a two-part design, were derived from an anatomical study of the vaginal and target geometry in 90 patients [57]. Several design iterations were created and 3D printed. Every design change was related to verifications in a design history flowchart. In the final embodiment design (Fig. 2), applicator halves are connected to a Geneva tandem (Elekta AB, Stockholm, Sweden) with a form-fit and snap-fit mechanism. A swept tapered section connects the patient-tailored top to a 25 (or 28) mm circular entry region. Standard entry configurations provide up to six (or eight) IS needles to be inserted per half. ProGuide 6F needles and obturators (Elekta AB) are guided through 3.0 mm diameter channels and can be locked with needle lock pins (Elekta AB) in dedicated templates [58]. Dwell positions in the IS needles at a distance of 6 mm to the top surface are used to mimic a conventional ring structure [55]. The halves also include tapered channel ends (to 2.4 mm for improved needle guidance), a dedicated channel that facilitates insertion of ultrasound gel for applicator reconstruction [39], and an extruded patient identification number. Descriptions of product features, accessories, and materials were documented.

For the MDSW, core modules were designed that handled data initialisation, geometry processing, catheter planning and geometric coverage-based selection, dwell-time optimisation and configuration evaluation, and export. The largely automated workflow was aligned with the current clinical workflow and uses additional user input especially for quality control as to mitigate risks. In addition, automated verification tests were devised for each module. Inputs of the MDSW are obtained from Oncentra Brachy (version 4.6, Elekta AB) and MIM (version 7.1, MIM Software Inc., Beachwood, OH, U.S.A), and include: (i) delineations of target volumes, organs at risk (OARs), and the vaginal cavity (RTStruct file), (ii) MR images, (iii) treatment plan (RTPlan file), and (iv) conventional applicator data (XML files). The software exports among others treatment plans, CAD data (STL files for 3D printing, and XML files for library-based reconstruction [59]), and plan reports (e.g., dosimetry tables, slice views, and needle insertion sheets). Changes in the code were tracked by using Git and linked to requirements and risks with unique IDs.

3.4. *Manufacturing and verification*

ARCHITECT applicators are 3D printed on a Formiga P1 system (EOS, Krailling, Germany) using PA-12 (EOS PA 2200) by Oceanz (Ede, the Netherlands). The material and printing technique were selected considering biocompatibility (EN ISO 10993–1:2018), sterilisability, and mechanical properties. Prints and channels are cleaned with manual, pressurised air, and ultrasonic cleaning, and post-processed with vapour treatment (AMT PostPro SFX, Veszprém, Hungary) to ensure smooth surfaces. Procedures and quality control actions are standardised. Cleaning, thermal disinfection, and sterilisation (autoclaving at 134 °C, 3.04 bar for 4 min.) are performed in accordance with in-hospital guidelines.

MDSW code was implemented in MATLAB (R2021b, MathWorks, Natick, Massachusetts, USA) and uses command-line user inputs (Fig. 2). The software runs on the computing cluster of Erasmus MC and uses Erasmus RTStudio, which is an in-house developed radiotherapy software package built on the MatterhornRT platform. Access to the software is restricted to authenticated medical personnel, and all computations are performed on pseudonymised data. For complex operations, the use of software of unknown provenance (SOUPs) was minimised and limited to well-tested functions. Automated multi-criteria dwell-time optimisation is performed with the in-house developed optimiser BiCycle [32,60,61]. For geometry processing, three toolboxes are used: gptoolbox, GIBBON, and MeshFix [62–64]. A QMS is available in the web application Redmine. In case of a task, bug or issue, the user can request changes. The developer can subsequently modify a local copy of the code, perform automated testing on a subset of cases, and commit the code to the Git repository. The Redmine platform notifies the user of the changes and keeps track of modifications to the software.

Verifications (Fig. 3) showed that intended performance and safety were achieved after several design iterations. Patient-tailored applicator configurations were non-inferior and, in selected cases, improved dosimetry compared to clinically used configurations in a simulated cohort of 22 patients (Fig. 3a) [40]. In this cohort patient-tailored configurations resulted in increased adherence to planning aims and significantly improved $\mathrm{CTV_{IR}}$ D_{98} while reducing bladder $D_{2\mathrm{cm}^3}$. In addition, we verified our software's functioning in a larger dataset of 85 patients. Planning aim attainment improved with the ARCHITECT configurations, and potential trade-offs between the number of needle channels and plan quality were observed [65]. In a pelvic phantom study, radiation oncologists found the prototype intuitive and easy to use, but noted that needle insertion required excessive force and that greater stiffness was needed at the applicator's distal ends (Fig. 3b). This led to a redesign of the needle fixation template and an increase in channel diameter (to 3.0 mm). Mechanical evaluations were conducted and led to a reduction of the distal end lengths and extension of applicator body to ensure adequate stiffness. Connections with other parts, including tandem and needle lock pins, were shown to not fail after 100 mating cycles. No obstructions of the Flexisource (Elekta AB) dummy cable were observed when bending ProGuide 6F (Elekta AB) catheters to the maximum curvature specified by the manufacturer (13 mm), which is higher than the curvature constraint used in the MDSW. Results from insertion force experiments and simulations indicated that channel lumen of 3 mm and maximum bending radii of 50 mm limited needle insertion forces sufficiently [39,66]. Needle deflections from the centreline amounted to 1.6–6.1 mm at 50 mm depth in phantom measurements, depending on the insertion angle (Fig. 3c). Simulation results suggested that at smaller deviations from the tissue normal, deflections were primarily driven by channel lumen diameter and curvature. To

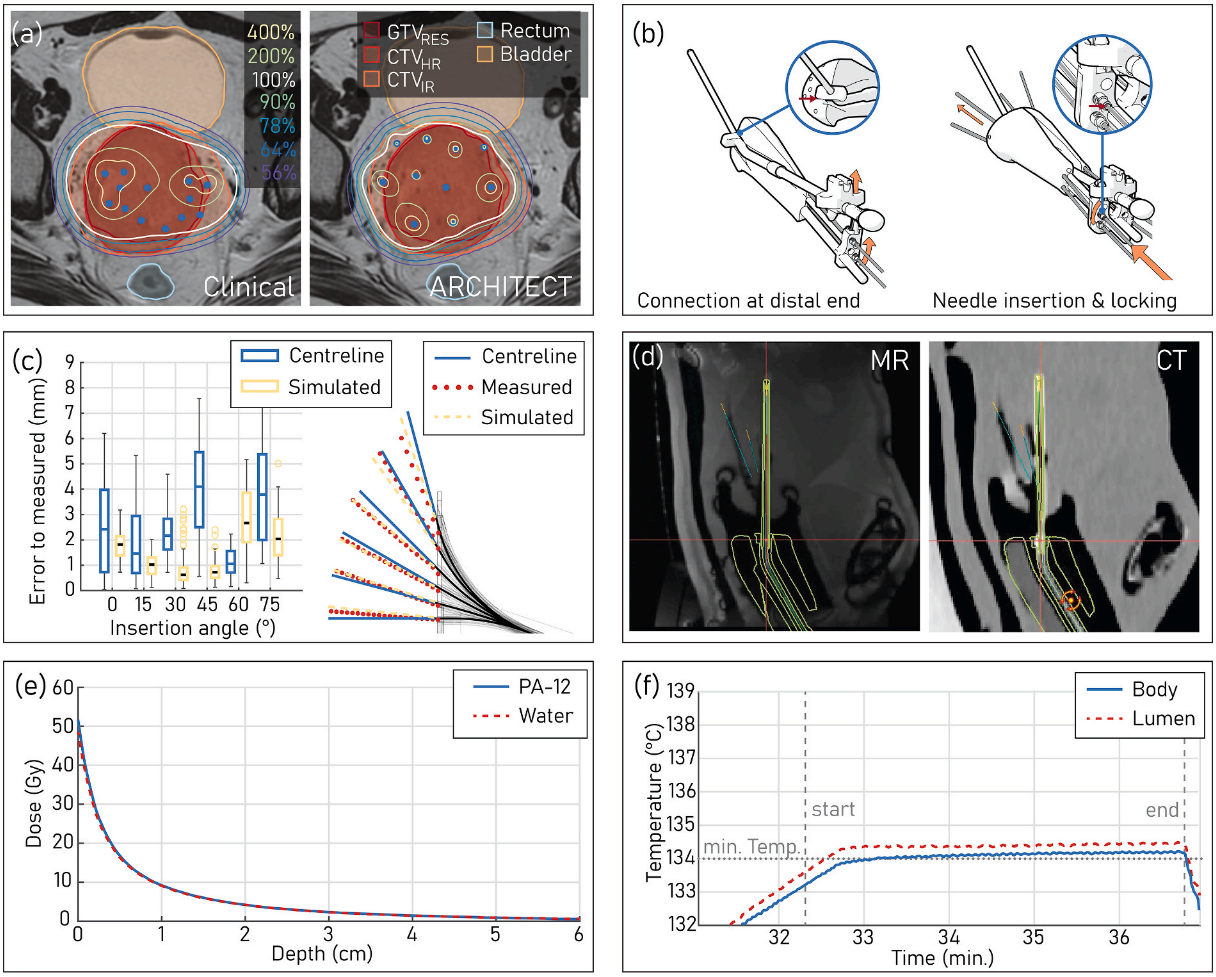


Fig. 3. Summary of verification results for the ARCHITECT applicator and software (see Supplementary Table S.1). (a) Dosimetric comparison in a complex patient case (FIGO IIIC2, T2a2N1M0, treated with 4 BT fractions) as part of a virtual planning study showed a 1.3 Gy increase in CTV$_{HR}$ D_{90} with no change in OAR D_{2cm^3} doses. (b) Phantom study feedback by radiation oncologists highlighted distal-end stiffness and ease of needle insertion. (c) Needle deflections for varying insertion angles. (d) Library-based reconstruction of the applicator on MR and CT. (e) Dose-depth curves for PA-12 and control/water (TG-43) setups. (f) Temperature profiles during 134 °C, 3.04 bar steam sterilisation from thermocouples at the applicator body and within the channel lumen.

limit deflections to acceptable levels (<5 mm, i.e., the margin taken into account by the MDSW), further tapering of the channels, reduction in channel curvature, and restriction of insertion angles (<75° with respect to surface normal) were therefore necessary. Reconstruction of the ARCHITECT applicator on MR imaging using library models in Oncentra Brachy (Elekta AB) and a line marker in the tandem was feasible (Fig. 3d), and resulted in an average dwell position error of 1.7 mm (including uncertainty due to rigid registration, slice thickness and transport) between CT and MR. To improve visibility of the applicator halves, dedicated channels were added in which ultrasound gel can be inserted.

Several material verifications were performed. Biological safety risks of the MD were found to be negligible based on biocompatibility test reports from the material supplier, reported data, and cytotoxicity testing (ISO 10993–5:2009) on the final product. Average dose depth curves of PA-12 and water were furthermore within 1% at 1 to 6 cm from the source channel as determined from Gafchromic film (Fig. 3e) [38]. Based on data from the material supplier, a single steam sterilisation procedure at 134 °C, 3.04 bar for 4 min did not detriment mechanical properties of PA-12 samples and achieved sterility (EN ISO 11737–1:2018). Thermocouple measurements on the surface and in the lumen of the applicator showed that these reached the required temperature of 134 °C for at least 3 min. (Fig. 3f). As the narrow channels pose risks for cleaning and sterilisation, custom cleaning connectors and sterilisation trays were developed. The risks were re-evaluated after verifications, and rationales were written for the residual risks that had been reduced to the lowest practicable level but were not fully resolved. This was the case for 7 risks, including PA-12 powder release, improper cleaning and sterilisation of the needle channels, excessive needle insertion forces and deflections, and prolonged duration of treatment. In all cases, potential benefits were deemed to outweigh these residual risks.

For each individual 3D printed applicator, additional quality assurance procedures are implemented alongside the standard QMS of the 3D print supplier and our routine BT workflow. Following design in the MDSW, the predicted dose distribution and needle geometry are reviewed and compared to that of the clinically used configuration by the BT team in MIM software. A medical physicist visually inspects the generated STL for accuracy of connecting interfaces, surface smoothness, and minimum wall thickness. After manufacturing, internal channels are cleared of excess PA-12 powder by the supplier using pressurised air, ultrasonic cleaning, and manual brushing. Upon product receipt in the hospital, inspection is performed by a medical physics assistant. Applicator channels are cleaned with brushes to confirm complete removal of residual powder. Moreover, correct interfacing with the intrauterine tandem is verified, and smooth needle insertion and locking are validated. Unobstructed source traversal is assessed with the Source Position Check Ruler (Elekta AB). Finally, the dimensional accuracy of the applicator body (width and length) is determined using callipers, and channel positions are compared with those of the virtual model with a printout. When no gross deviations, e.g., due to patient or needle configuration mix-ups, are identified, approval for use is granted.

4. Discussion

In this work, we present the in-house development of a patient-tailored BT applicator with dedicated software, compliant with MDR requirements for clinical investigations. A systematic and risk-based design approach was considered, linking process steps to requirements, (design) characteristics for safety, risks and control measures, design versions, and product verification activities. To demonstrate safety and performance of the medical device including software, a series of pre-clinical verifications was performed. By preparing the relevant QMS procedures and templates, we initiated the technical documentation required for clinical investigations or in-house use in accordance with MDR Article 5(5). Finalisation of the IMDD is pending for submission to the institutional review board.

The MDR has a profound impact on the introduction, continuation, and availability of in-house developed medical devices in Europe. In particular, research support, protected time, and regulatory expertise are all needed to overcome these barriers, as also identified within ESTRO and other working groups [13,67]. In addition, a commonly discussed challenge is whether regulatory approval is required and whether to pursue it for simple assistive tools, such as spreadsheets performing calculations. At our institute, regulatory knowledge was acquired and QMS procedures implemented alongside this project, while other MDR-compliant medical devices were simultaneously developed [32]. Nevertheless, the development of the medical device and the documentation process was lengthy, lasting ~24 months alongside other research activities by two full-time researchers. Similarly, other studies have demonstrated that in-house development procedures often involve substantial time and cost investments [32,68]. In our case, we benefitted from selecting a 3D print supplier with a QMS system (EN ISO 13485:2016) in place. Point-of-care (in-house) 3D printing potentially reduces turnaround time and costs [30], but since an appropriate QMS for the manufacturer is mandated, only a limited number of centres in Europe are currently equipped for these procedures. To facilitate widespread adoption of in-house development, researchers are encouraged to document workflows and verification steps, and share experiences for development of best practices.

Although flowcharts in this work and others are often presented as linear frameworks [13,69], the development of medical devices in general is complex and involves multiple iterations [31,70]. Our applicator prototype underwent nine major iterations, which were for example based on risk evaluations, verification tests, and processing constraints. As prospective risk management is mandated by the MDR –as well as by the Directive 2013/59/Euratom [11]–, it can be put at the core of the design, manufacturing and verification phases [18]. This can be achieved with an integrated development approach in which procedural steps, requirements, (design) characteristics for safety, risk management, and evaluations are tightly coupled, as was implemented in this work. For MDSW, the IEC 62304:2015 standard already mandates such an integrated approach in which software requirements, design elements, and verifications are directly linked to risks. A corresponding framework for traceability had already been established in our department for another MDSW application [32]. However, there are some challenges in prospective risk management of medical devices. Previous surveys in radiotherapy have indicated that there are large disparities in institutes in the application and knowledge gaps of risk management [71,72]. In addition, risk management requires a multidisciplinary perspective and can be time-consuming. And lastly, whereas the EN ISO 14971:2019 framework has been harmonised to the MDR, risk management in medical physics applications is often performed using failure mode and effects (FMEA) or fault tree analyses, which only partially address the former [51]. Therefore, we initiated our analysis by adapting from existing terminology and FMEA analyses [47,73,74], but used the EN ISO 14971:2019 framework.

The in-house MDR exemption is only justified in case no commercially available device can (be modified to) meet desired target needs or performance. Similarly, custom-made devices can address individual patient needs, require a written prescription (i.e., statement by an authorised healthcare professional) and are exempt from certain MDR obligations [26]. In case of the latter, Article 52(8) of the MDR applies, requiring among others a QMS (Article 10(9), MDR), and compliance with GSPRs (Annex I, MDR) and device-specific procedures (Annex XIII, MDR) [1,41]. As detailed in MDCG 2023-1, custom-made devices are out of scope of the in-house exemption [27], although it remains unclear which pathway applies when such devices are manufactured within a health institution [26]. In addition, by definition of MDCG 2021–3, custom-made medical devices are to be distinguished from 'adaptable' (i.e., mass-produced), or 'patient-matched' (i.e., matched within a design envelope) medical devices [41]. Although the patient-tailored applicator discussed in this work is adapted to the patient's anatomy, this procedure is performed by the MDSW following standardised rules and is based on a combination of template models and files of the patient. Similarities to the examples given in MDCG 2021–3 lead us to classify it as patient-matched rather than custom-made. Patient-tailored 3D printed cervical cancer BT applicators with custom needle configurations can achieve better target coverage and OAR sparing than commercial applicators typically in patients with large target volumes or complex geometries [40]. Therefore, custom needle geometries may be favourable for 20–30% of all applications [56,75]. In addition, 3D printing can be used to accommodate for patients with a narrow vagina or related indications that cannot be treated with conventional devices [56]. And lastly, 3D printing may provide a cost benefit, although this is not considered a valid justification for the Article 5(5) exemption [27]. However, 3D printing comes with challenges related to medical device design (e.g., time and experience of staff), manufacturing (e.g., tolerances, post-processing, and quality assurance), and material properties (e.g., mechanical, dose attenuation, biocompatibility, sterilisation, and imaging properties). Several papers have therefore proposed verification methods [36–38], which are similar to the ones presented here. Standardisation and reporting of verification tests can help distribute the burden associated with the development of these medical devices and to maintain overall cost-effectiveness.

There are several limitations to this study. In this work, we outline our efforts to set up technical documentation as required for clinical investigation (IMDD) of an in-house developed medical device, anticipating the Article 5(5) MDR exemption. This means that clinical evaluation (validation phase) to verify safety and performance of the medical device (Article 61, MDR) and corresponding documentation were outside the scope of this paper. Our planned clinical investigation is a prospective, non-randomised feasibility trial in 25 patients, with secondary aims to assess plan quality, configuration geometry, adverse events, workflow, and user and patient experience. The first application in each patient will be performed with a standard commercial applicator, followed by use of the patient-tailored applicator in subsequent applications. Approval by the medical ethics committee is pending. Considerations for clinical evaluation of medical devices have previously been described [76], and a summary of an IMDD is provided by Willemsen et al. [29]. In brief, in most cases clinical evaluation requires clinical investigation (Articles 62, 74 or 82, and Annex XV) [43]. For in-house developed medical devices, Article 62 or 82 applies depending on the aim of the investigation and national guidelines [26]. Clinical investigation in practice follows guidelines on good clinical practices (see Recital 64 of the MDR, which e.g. lists EN ISO 14155:2020 [77], and the Declaration of Helsinki). Materials required for review by the institutional review board in the Netherlands then include: (a) the clinical investigation plan (including research protocol and study-specific information, e.g., informed consent forms), (b) product information (including the IMDD and instructions for use), and (c) supporting materials (including documents listed by Chapter II, Annex XV of the MDR). Also post-investigational use aspects were not discussed here, such as routine collection and review of data gained during clinical use, and user training. Moreover, next to the pre-clinical verifications shown here, we plan to conduct a dry-run evaluation parallel to the clinic. This includes applicator planning, manufacturing and post-processing, transport and storage, and cleaning and sterilisation. As applicator planning procedures are almost fully automated, and other steps align with our current clinical practice, we do not anticipate large interferences with the existing workflow, which has been previously described [78]. Lastly, the regulatory framework under the MDR is complex and dynamic, as also evidenced by ongoing implementation and interpretation documents by the MDCG, as well as continuous harmonisation and updates of standards. For in-house developed and 'investigational' medical devices –particularly those in lower risk classes– we feel that proportionality applies when considering the regulations and standards, for example with regards to complexity of documentation, the used QMS, and verifications [26]. Within this context, the MDR represents the primary regulatory framework, and harmonised standards constitute the maximum practical level of alignment. Other non-harmonised or general standards can be adopted only when they directly apply to specific device types. In many cases we could offset risks by relying on standard, certified systems and workflows. As such, for several steps we adopted 'light' approaches, for example in the development of the MDSW by: (i) having concise documentation and using incremental coding, opposed to basing this on a detailed software development plan, (ii) using basic verification testing rather than multi-level testing, and (iii) applying simple version control rather than formal configuration management. MDR-compliant in-house manufacturing should ensure safety and performance, whilst allowing the flexibility to adapt to clinical needs, consistent with the principles of Article 5(5).

5. Conclusions

Medical devices manufactured and used in health care institutions in Europe must comply with the MDR. In this work we documented the MDR-compliant development of a patient-tailored cervical cancer brachytherapy applicator and dedicated software for use within a clinical study. We detailed our procedures, along with the relevant MDR articles, annexes, and standards, to guide researchers and developers pursuing similar in-house development. A series of verifications demonstrated adherence of the device to the general safety and performance requirements. Even under the Article 5(5) exemption, documentation of regulatory aspects related to medical device development is complex and entails a significant workload. This highlights the need for involvement of multi-disciplinary stakeholders during the entire process, as well as providing researchers and developers with adequate infrastructural and regulatory support. Researchers and developers are encouraged to document similar efforts and share experiences for generation of best practices for future in-house development of medical devices.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejmp.2026.105783.

References

[1] Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices, amending Directive 2001/83/EC, Regulation (EC) no 178/2002 and Regulation (EC) no 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC., (2017).

[2] Council Directive 93/42/EEC of 14 June 1993 concerning medical devices, (1993).

[3] Council Directive 90/385/EEC of 20 June 1990 on the approximation of the laws of the Member States relating to active implantable medical devices, (1990).

[4] Niemiec E. Will the EU medical device regulation help to improve the safety and performance of medical AI devices? Digit Health 2022;8:20552076221089079.

[5] Schmitz AA, Font-Nieves M, Doucoure T, Podhaisky HP. Impact of Rule 11 on the European medical software landscape: analysis of EUDAMED and further databases three years after MDR implementation. Ther Innov Regul Sci 2025;59(2):365–78.

[6] Melvin T. The European medical device regulation-what biomedical engineers need to know. IEEE J Transl Eng Health Med 2022;10:4800105.

[7] Bretthauer M, Gerke S, Hassan C, Ahmad OF, Mori Y. The new European medical device regulation: balancing innovation and patient safety. Ann Intern Med 2023;176(6):844–8.

[8] European Commission. Guidance - MDCG endorsed documents and other guidance 2025 [Available from: https://health.ec.europa.eu/medical-devices-sector/new-regulations/guidance-mdcg-endorsed-documents-and-other-guidance_en].

[9] European Commission. Harmonised Standards 2025 [Available from: https://health.ec.europa.eu/medical-devices-topics-interest/harmonised-standards_en].

[10] Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on in vitro diagnostic medical devices and repealing Directive 98/79/EC and Commission Decision 2010/227/EU (Text with EEA relevance), (2017).

[11] Council Directive 2013/59/Euratom of 5 December 2013 laying down basic safety standards for protection against the dangers arising from exposure to ionising radiation, and repealing Directives 89/618/Euratom, 90/641/Euratom, 96/29/Euratom, 97/43/Euratom and 2003/122/Euratom, (2013).

[12] Regulation (EU) 2024/1689 of the European Parliament and of the Council of 13 June 2024 laying down harmonised rules on artificial intelligence and amending Regulations (EC) No 300/2008, (EU) No 167/2013, (EU) No 168/2013, (EU) 2018/858, (EU) 2018/1139 and (EU) 2019/2144 and Directives 2014/90/EU, (EU) 2016/797 and (EU) 2020/1828 (Artificial Intelligence Act) (Text with EEA relevance), (2024).

[13] Beckers R, Kwade Z, Zanca F. The EU medical device regulation: implications for artificial intelligence-based medical device software in medical physics. Phys Med 2021;83:1–8.

[14] Cosgriff PS, Memmott MJ. Writing in-house medical device software in compliance with EU, UK, and US regulations. In: 2385 NW Executive Center Drive, Suite. 1st ed.320. Boca Raton FL 33431: CRC Press; 2024.

[15] Directive (EU) 2024/2853 of the European Parliament and of the Council of 23 October 2024 on liability for defective products and repealing Council Directive 85/374/EEC (Text with EEA relevance), (2024).

[16] Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (Text with EEA relevance), (2016).

[17] Hwang TJ, Sokolov E, Franklin JM, Kesselheim AS. Comparison of rates of safety issues and reporting of trial outcomes for medical devices approved in the European Union and United States: cohort study. BMJ 2016;353:i3323.

[18] Miclaus T, Valla V, Koukoura A, Nielsen AA, Dahlerup B, Tsianos GI, et al. Impact of design on medical device safety. Ther Innov Regul Sci 2020;54(4):839–49.

[19] White NA, Oude Vrielink TJC, van der Bogt; KEA, Cohen AF, Rotmans JI, Horeman T. Question-based development of high-risk medical devices: a proposal for a structured design and review process. Br J Clin Pharmacol 2023;89(7):2144–59.

[20] Jarman H, Rozenblum S, Huang TJ. Neither protective nor harmonized: the crossborder regulation of medical devices in the EU. Health Econ Policy Law 2021;16(1):51–63.

[21] Ben-Menahem SM, Nistor-Gallo R, Macia G, von Krogh G, Goldhahn J. How the new European regulation on medical devices will affect innovation. Nat Biomed Eng 2020;4(6):585–90.

[22] MedTech Europe. MedTech Europe Survey Report analysing the availability of Medical Devices in 2022 in connection to the Medical Device Regulation (MDR) implementation. 2022.

[23] Horst A, McDonald F. Uncertain but not Unregulated: Medical Product Regulation in the Light of Three-Dimensional Printed Medical Products. 3D Print Addit Manuf 2020;7(5):248–57.

[24] de Jong IJ, Lexis MAS, Slegers K, Tuijthof GJM. Medical device regulation: requirements for occupational therapists in the Netherlands who prescribe and manufacture custom-made devices. Disabil Rehabil Assist Technol 2024;19(4):1415–23.

[25] Pettersson ABV, Ballardini RM, Mimler M, Li P, Salmi M, Minssen T, et al. Core legal challenges for medical 3D printing in the EU. Healthcare (Basel) 2024;12(11).

[26] Boyle G, Melvin T, Verdaasdonk RM, Van Boxtel RA, Reilly RB. Hospitals as medical device manufacturers: keeping to the Medical Device Regulation (MDR) in the EU. BMJ Innov 2024;10(3):74–80.

[27] Medical Device Coordination Group. Guidance on the health institution exemption under Article 5(5) of Regulation (EU) 2017/745 and Regulation (EU) 2017/746 2023.

[28] Zanca F, Brusasco C, Pesapane F, Kwade Z, Beckers R, Avanzo M. Regulatory aspects of the use of artificial intelligence medical software. Semin Radiat Oncol 2022;32(4):432–41.

[29] Willemsen K, Nizak R, Noordmans HJ, Castelein RM, Weinans H, Kruyt MC. Challenges in the design and regulatory approval of 3D-printed surgical implants: a two-case series. Lancet Digit Health 2019;1(4):e163–71.

[30] Poppe JP, Spendel M, Griessenauer CJ, Gaggl A, Wurm W, Enzinger S. Point-of-care 3-dimensional-printed polyetheretherketone customized implants for cranioplastic surgery of large skull defects. Oper Neurosurg (Hagerstown) 2024;27(4):449–54.

[31] van Kempen EB, Vrijlandt SEW, van der Geest K, Lotgering S, Hueting TA, Oostenbrink R. A blueprint for clinical-driven medical device development: the feverkidstool application to identify children with serious bacterial infection. Mayo Clin Proc Digit Health 2024;2(4):656–64.

[32] Kolkman-Deurloo IK, Rossi L, Zolnay A, Christianen M, Westerveld H, Luthart L, et al. PHSOR07 presentation time: 9:30 am: in-house developed medical device software bicycle for automated BT treatment planning, compliant with the european medical device regulation (MDR). Brachytherapy 2024;23(6).

[33] Barten DLJ, Pieters BR, Bouter A, van der Meer MC, Maree SC, Hinnen KA, et al. Towards artificial intelligence-based automated treatment planning in clinical practice: a prospective study of the first clinical experiences in high-dose-rate prostate brachytherapy. Brachytherapy 2023;22(2):279–89.

[34] Vandewinckele L, Benazzouz C, Delombaerde L, Pape L, Reynders T, Van der Vorst A, et al. Pro-active risk analysis of an in-house developed deep learning based autoplanning tool for breast volumetric modulated arc therapy. Phys Imaging Radiat Oncol 2024;32:100677.

[35] Lagerburg V, van den Boorn M, Crane RF, Welvaars K, Groen JM. Applying and validating a quality management system for in-house developed medical software. Front Digit Health 2025;7:1461107.

[36] McGarry CK, Tonino Baldion A, Burnley J, Byrne N, Doolan PJ, Jenkins R, et al. IPEM topical report: guidance on 3D printing in radiotherapy. Phys Med Biol 2025;70(4).

[37] Ashenafi M, Jeong S, Wancura JN, Gou L, Webster MJ, Zheng D. A quick guide on implementing and quality assuring 3D printing in radiation oncology. J Appl Clin Med Phys 2023;24(11):e14102.

[38] Cunha JA, Mellis K, Sethi R, Siauw T, Sudhyadhom A, Garg A, et al. Evaluation of PC-ISO for customized, 3D Printed, gynecologic 192-Ir HDR brachytherapy applicators. J Appl Clin Med Phys 2015;16(1):5168.

[39] Laan RC, Nout RA, Dankelman J, van de Berg NJ. MRI-driven design of customised 3D printed gynaecological brachytherapy applicators with curved needle channels. 3D Print Med 2019;5(1):8.

[40] Straathof R, van Vliet-Pérez SM, Kolkman-Deurloo IK, Wauben L, Nout RA, Heijmen BJM, et al. Automated planning of curved needle channels in 3D printed patient-tailored applicators for cervical cancer brachytherapy. Phys Med Biol 2024;69(23).

[41] Medical Device Coordination Group. Questions and Answers on Custom-Made Devices & considerations on Adaptable medical devices and Patient-matched medical devices. 2021.

[42] Medical Device Coordination Group. Medical Device Software (MDSW) - Hardware Combinations Guidance on MDSW intended to work in combination with hardware or hardware components. 2023.

[43] Medical Device Coordination Group. Regulation (EU) 2017/745 - Questions & Answers regarding clinical investigation. 2021.

[44] International Organization for Standardization (ISO). ISO 10993-1:2018: Biological evaluation of medical devices. Part 1: Evaluation and testing within a risk management process. 2018.

[45] International Electrotechnical Commission (IEC). IEC 62366-1:2015: Medical devices. Part 1: Application of usability engineering to medical devices. 2015.

[46] Roozenburg NFM, Eekels J. Product design: fundamentals and methods. Chichester: Wiley; 1995.

[47] Huq MS, Fraass BA, Dunscombe PB, Gibbons Jr JP, Ibbott GS, Mundt AJ, et al. The report of Task Group 100 of the AAPM: Application of risk analysis methods to radiation therapy quality management. Med Phys 2016;43(7):4209.

[48] Medical Device Coordination Group. Guidance on classification of medical devices. 2021.

[49] International Electrotechnical Commission (IEC). IEC 62304:2006/Amd 1:2015: Medical device software - Software life cycle processes - Amendment 1. 2015.

[50] International Organization for Standardization (ISO). ISO 14971:2019: Medical devices - Application of risk management to medical devices. 2019.

[51] International Organization for Standardization (ISO). ISO/TR 24971:2020: Medical devices - Guidance on the application of ISO 14971. 2020.

[52] International Organization for Standardization (ISO). ISO 13485:2016: Medical devices - Quality management systems - Requirements for regulatory purposes. 2016.

[53] Potter R, Tanderup K, Kirisits C, de Leeuw A, Kirchheiner K, Nout R, et al. The EMBRACE II study: the outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. Clin Transl Radiat Oncol 2018;9:48–60.

[54] Petric P, Hudej R, Al-Hammadi N, Segedin B. Virtual modelling of novel applicator prototypes for cervical cancer brachytherapy. Radiol Oncol 2016;50(4):433–41.

[55] Serban M, Fokdal L, Nielsen SK, Hokland SB, Hansen AT, Spejlborg H, et al. Characterization of combined intracavitary/interstitial brachytherapy including oblique needles in locally advanced cervix cancer. Brachytherapy 2021;20(4):796–806.

[56] Cobussen A, Petric P, Wulff CN, Buus S, Spejlborg H, Nielsen SK, et al. Clinical outcomes using a 3D printed tandem-needle-template and the EMBRACE-II planning aims for image guided adaptive brachytherapy in locally advanced cervical cancer. Acta Oncol 2023;62(11):1470–8.

[57] van Vliet-Pérez S, Straathof R, Westerveld H, van de Berg N, Dankelman J, Wauben L, et al. PO0249: assessment of anatomical variation for patient-tailored cervical cancer brachytherapy applicator development. Brachytherapy 2024;23(6).

[58] de Ridder M, Smolic M, Kastelijns M, Kloosterman S, van der Vegt; S, Rijken JA, et al. Individualized 3D-printed applicators for magnetic resonance imaging-guided brachytherapy in nasal vestibule cancer. Phys Imaging Radiat Oncol 2024;31:100629.

[59] Otal A, Richart J, Rodriguez S, Santos M, Perez-Calatayud J. A method to incorporate interstitial components into the TPS gynecologic rigid applicator library. J Contemp Brachyther 2017;9(1):59–65.

[60] Rossi L, Bijman R, Chopra S, Mittal P, Panda S, Westerveld H, et al. Rule-based AI automated adaptive treatment planning for image guided cervical cancer brachytherapy. Brachytherapy 2025.

[61] Rossi L, Bijman R, Westerveld H, Christianen M, Luthart L, Huge M, et al. Prospective evaluation of AI-based BiCycle autoplanning for advanced cervical cancer brachytherapy. Radiother Oncol 2025;210:111029.

[62] Jacobson A., et al. Geometry Processing Toolbox. https://github.com/alecjacobson/gptoolbox.

[63] Moerman KM. GIBBON: the geometry and image-based bioengineering add-on. J Open Source Software 2018;3(22):1–4.

[64] Attene M. A lightweight approach to repairing digitized polygon meshes. Vis Comput 2010;26(11):1393–406.

[65] van Vliet-Pérez SM, Straathof R, Westerveld H, van De Berg NJ, Dankelman J, Wauben L, et al. Treatment plan evaluation of the patient-tailored ARCHITECT applicator for cervical cancer brachytherapy. AAPM 67th Annual Meeting & Exhibition; Washington, DC, USA. 2025.

[66] Straathof R, Meijaard JP, van Vliet-Pérez SM, Kolkman-Deurloo IK, Nout RA, Heijmen BJM, et al. Multibody dynamic modeling of the behavior of flexible instruments used in cervical cancer brachytherapy. Med Phys 2024;51(5):3698–710.

[67] ESTRO Working Group on Priorities of ESTRO for engagement within the EURAMED framework. Priorities of ESTRO for engagement within the EURAMED framework 2025 [Available from: https://www.estro.org/About/Newsroom/Newsletter/Research-Projects/Priorities-of-ESTRO-for-engagement-within-the-EURA].

[68] Remeijer P. Is in-house development cost effective? ESTRO 2025; Vienna, Austria2025.

[69] Buist M, Ortiz-Catalan M. Engineering a quality management system for academic research: navigating challenges to comply with the new medical device regulations in Europe. Med Devices (Auckl) 2025;18:137–47.

[70] de Visser SJ, Cohen AF, Kenter MJH. Integrating scientific considerations into R&D project valuation. Nat Biotechnol 2020;38(1):14–8.

[71] Brouwer CL, Dinkla AM, Vandewinckele L, Crijns W, Claessens M, Verellen D, et al. Machine learning applications in radiation oncology: current use and needs to support clinical implementation. Phys Imaging Radiat Oncol 2020;16:144–8.

[72] Baehr A, Hummel D, Gauer T, Oertel M, Kittel C, Loser A, et al. Risk management patterns in radiation oncology-results of a national survey within the framework of the Patient Safety in German Radiation Oncology (PaSaGeRO) project. Strahlenther Onkol 2023;199(4):350–9.

[73] Mayadev J, Dieterich S, Harse R, Lentz S, Mathai M, Boddu S, et al. A failure modes and effects analysis study for gynecologic high-dose-rate brachytherapy. Brachytherapy 2015;14(6):866–75.

[74] Swamidas J, Khanna N, Mahantshetty U, Somesan V, Deshpande DD, Shrivastava SK. Implementation of failure mode and effective analysis for high dose rate brachytherapy at Tata Memorial Hospital, Mumbai. India Cancer Radiother 2018;22(4):334–40.

[75] Niedermayr T, Kidd E. Adaptive 3D-printed needle guides in IC/IS gynecological implants: cost and benefit in clinical use. Brachytherapy 2023;22(5):S75–6.

[76] Ecker W. Clinical evaluation and clinical investigations of medical devices under the MDR. In: Baumgartner CH, Johann SJ, editors. Medical Devices and In Vitro Diagnostics. Springer; 2023. p. 217–51.
[77] International Organization for Standardization (ISO). ISO 14155:2020: Clinical investigation of medical devices for human subjects - Good clinical practice. 2020.
[78] van Vliet-Pérez SM, van Paassen R, Wauben L, Straathof R, van de Berg NJ, Dankelman J, et al. Time-action and patient experience analyses of locally advanced cervical cancer brachytherapy. Brachytherapy 2024;23(3):274–81.