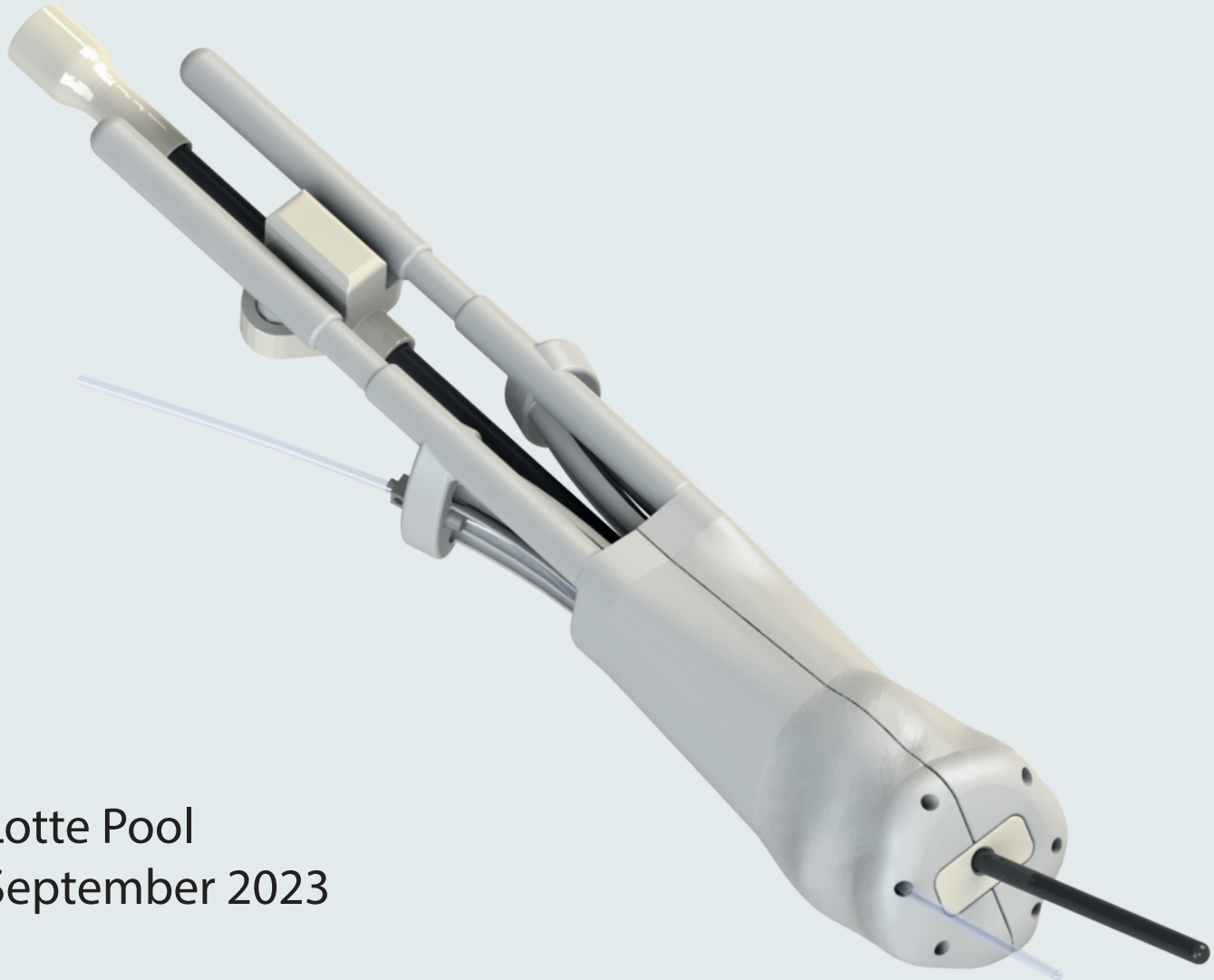
Design of a patient-tailored 3D-printed HDR brachytherapy applicator for the treatment of cervical cancer



Lotte Pool
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TU Delft

Design of a patient-tailored 3D-printed HDR brachytherapy applicator for the treatment of cervical cancer

by

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TU Delft

Erasmus MC
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Preface

This master's thesis marks the end of my time as a student. I am proud of the knowledge I have gained and of the project outcome, despite the ups and downs along the way. I would like to use this preface to thank everyone who helped me during the project and supported me.

First of all, I would like to thank my daily supervisor Robin Straathof for giving me the opportunity to graduate on this assignment and for guiding me though the whole process. Our weekly meetings, his advice and his extensive feedback have been very valuable. In addition, I would like to express my gratitude to my supervisors Nick van de Berg and Jenny Dankelman for their guidance and feedback.

I would like to thank the members of the ARCHITECT-project group for their feedback and letting me attempt their monthly meetings. These meetings have helped me learn a lot about the subject. Additionally, I would like to thank I. Kolkman-Deurloo for making it possible for me to attend the treatment procedure, arranging materials from the clinic when needed, and for her assistance in the planning and execution of the dosimetry experiment. Regarding this experiment, I would also like to express my gratitude to P. Baan who assisted in conducting the experiment and who provided me with an explanation about the film segments.

Furthermore, I would like to express my gratitude to the following people, whose contributions have facilitated the development of the risk analysis and/or the ability to make MRI/CT scans: S. van Vliet, R. Rijnsdorp, M. Huge, and L. Michielsen.

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Throughout the entire project, Oceanz has manufactured prototypes and Elekta has provided applicator demo models for analysis, both of which I am greatly thankful for.

Last but not least, I would like to thank my friends and family for their support and belief in me throughout the whole journey.

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Delft, September 2023

Abstract

Brachytherapy is a type of internal radiation therapy that is used to treat cervical cancer. It involves the application of a radioactive source in close proximity to the tumour. This can be done either by directly inserting the source into (or close to) the tumour using interstitial hollow needles, or by loading the source into an intracavitary applicator that is placed in the vaginal cavity. Standard applicator types may lead to suboptimal radioactive source placement, possibly resulting in underexposure of target volumes and overexposure of organs at risk, especially in advanced cancers. Customised applicators and optimised needle channels based on the patient's MRI/CT data could enhance conformity between target volumes and prescribed isodose. Hence, the goal of this project was to develop and validate a design for a 3D-printed brachytherapy applicator which geometry is based on the patient's vaginal cavity and which features optimised interstitial needle channels based on the patient's anatomy and tumour location.

Various analyses have been conducted which have led to the establishment of a list of requirements for the applicator design. Based on this list of requirements, two conceptual designs have been presented: one fully 3D-printed design and one design that is clicked on the Geneva ovoid tubes. Through the creation of prototypes, these conceptual designs have been refined into two final designs which were manufactured in PA12 using selective laser sintering. The dose attenuation properties of PA12 were evaluated and compared to that of water. Furthermore, the potential needle positions within the proximal end of both designs have been analysed. For both designs, a final prototype based on a phantom's vaginal cavity geometry has been created. The usability of these prototypes has been tested by three radiotherapist-oncologists, who also provided feedback on the designs. Upon analysing their feedback and the outcomes of the other evaluations, recommendations for future designs have been formulated.

The conducted dosimetry experiment yielded a maximum difference of 0.8% between the average percent dose depth curves of water and PA12, which can be considered a water-equivalent response. This allows PA12 to be used as the material for the applicator. The result of the potential needle position analysis suggest that the first design provides more space for personalised needle channels in the top of the applicator compared to the second design. The three radiotherapist-oncologists validated the usability of both final prototypes.

Two designs of a patient-tailored 3D-printed brachytherapy applicator containing optimised interstitial needle channels based on the patient's anatomy and tumour location have been presented, produced and validated. Based on the outcomes of the conducted evaluations, there can be concluded that the first concept shows the most promise to be used as a design for a patient-tailored 3D printed brachyhterapy applicator. However, to ensure the proper functioning of the working principles, further development is required. If the recommended improvements are implemented, the design has the potential to be used as applicator in the treatment of cervical cancer.

Contents

Abbreviations

FIGO	International Federation of Gynecology and Obstetrics
LACC	Locally advanced cervical cancer
EBRT	External beam radiation therapy
BT	Brachytherapy
OAR	Organs at risk
IC	Intracavitary
IS	Interstitial
IGBT	Image-guided brachytherapy
MRI	Magnetic resonance imaging
CT	Computed tomography
IGABT	Image-guided adaptive brachytherapy
GYN GEC-ESTRO	Gynaecological Working Group of the Groupe Européen de Curiethérapie of the European Society for Therapeutic Radiology and Oncology
GTV	Gross tumour volume
HR-CTV	High-risk clinical target volume
IR-CTV	Intermediate-risk clinical target volume
DVH	Dose volume histogram
LDR	Low-dose rate
PDR	Pulse-dose rate
HDR	High-dose rate
ABS	American Brachytherapy Society
MIM	Medical Image Merge
MDR	Medical Device Regulation
IMDD	Investigational Medical Device Dossier
ISO	International Organization for Standardization
AAPM	American Association of Physicists in Medicine

1 Introduction

1.1. Clinical introduction

Cervical cancer is a major cause of mortality and morbidity among women. It is the fourth most common cancer among women globally, with an estimated 604,000 new cases and 342,000 deaths in 2020 [1]. The extent of the disease is generally expressed in terms of its FIGO (International Federation of Gynecology and Obstetrics) stage, which determines the treatment method. The FIGO staging system ranges from stage I (the cancer is still just found in the uterus) to stage IVB (distant metastasis) [2]. Locally advanced cervical cancer (LACC) is a term used to distinguish cancers that have spread to outside of the cervix but not to major organs (FIGO stage IB2-IVA) and typically include bulky tumours (≥4cm in the diameter of tumour) [3, 4]. For the earliest stages of cervical cancer and favourable prognosis, either radiation combined with chemotherapy or surgery may be used as treatment. For later stages and LACC, radiotherapy with concurrent chemotherapy is the main treatment [5]. The most common and effective method of delivering radiotherapy is a combination of external beam radiotherapy (EBRT) and brachytherapy (BT).

Brachytherapy for cervical cancer involves the application of a radioactive source in close proximity to the tumour, either by directly inserting the source into or close to the tumour by the use of needles or by loading the source into a device placed in the vaginal cavity. Such a device is called an applicator. Due to the rapid dose fall off with increasing distance from the source, BT allows the delivery of very high radiation doses to the target region while retaining excellent sparing of the adjacent organs at risk (OAR): bladder, rectum, and sigmoid. Compared to EBRT alone, the inclusion of BT in the treatment of LACC has persistently shown to reduce local recurrence and to improve overall survival [6, 7].

1.2. Brachytherapy application techniques

BT can be categorised according to a number of factors, including the approach used to insert the sources into the patient and the rate at which radiation dose is delivered. Depending on the approach used to position the sources into the patient, BT can be divided into intracavitary, interstitial, and hybrid BT.

Intracavitary (IC) BT involves guiding the radioactive source through the applicator. In this way, the upper vagina, cervix, and uterus can be treated. Such an applicator usually contains an intrauterine component called a tandem, and two ovoids or a (split) ring, which are placed against the vaginal fornices (see Figure 1.1A). Vaginal packing may be placed in the vaginal cavity to stabilise the applicator. The radiation source is positioned in the tandem and ovoids/ring. Purely IC techniques are most suited for small tumours with no parametrial involvement (tumour confined to cervix) [8].

In interstitial (IS) BT, the radioactive source is placed in and/or around the tumour guided by hollow needles. The needles are guided though the applicator into the patient's tissue. IS BT requires a central structure (the tandem) for proper dose distribution. This BT technique is helpful in patients with bulky infiltrative extensive disease, recurrent disease, vaginal spread of the disease, or anatomical unfavourable topography such as a narrow vagina or asymmetrical tumour growth [9].

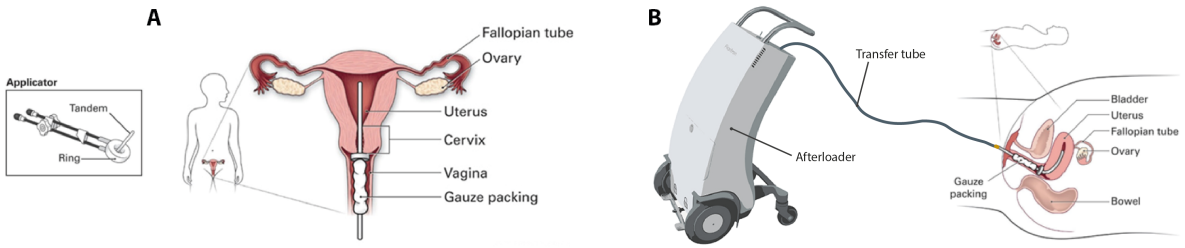


Figure 1.1: IC tandem and ring applicator in situ: (a) anterior view; (b) lateral view with location of the OARs: bladder, rectum and sigmoid. Adapted from [10].

Hybrid BT is a combination of the IC and IS techniques: IS needles are placed in combination with an IC applicator. These needles can be guided through holes in the ovoids or ring, by a template, or the needles can be placed without any guidance (free-hand needles). When guided through holes in the ring/ovoids, the needles can be inserted parallel or obliquely with fixed angles in relation to the tandem. IC BT alone results in a standard pear-shaped dose distribution. In large and/or irregularly shaped tumours or lower vaginal involvement, this may result in incomplete coverage of the target volume [11, 5]. The dose distribution can be modified through the addition of IS needles, hence hybrid BT can be used when IC BT alone results in incomplete coverage of the target volume. Currently, hybrid BT is the standard treatment technique.

The radiation during BT is delivered by a a physical radiation source encapsulated and housed in a device called an afterloader. Transfer tubes are connected from the inserted applicator and needles to the afterloader, as is shown in Figure 1.1B. During treatment, the source is driven out of the afterloader and steps to pre-determined positions within the applicator and needles. These positions are called dwell positions. The source stops at each dwell position for a precalculated length of time, called the dwell time, to deliver the radiation as is determined in the patient's treatment plan.

1.3. Dose prescription

The absorbed radiation dose is expressed in SI unit Gray (symbol Gy). Historically, BT was based on orthogonal 2D X-ray imaging in which the dose was prescribed to a virtual point A located at a fixed distance from the applicator. This dose prescription leads to a standard pear-shaped isodose distribution. In an isodose distribution lines delineate areas that receive the same dose. It is typically shown using a color-coded map, with different colors representing different dose levels.

In 2D BT, the dose distribution is independent of tumour size and topography, the response of the tumour to EBRT, and the dose that gets delivered to the OARs and thus depends solely on the used applicator/definition of point A. This may result in potential undertreatment and subsequently loss of local control. Local control is the absence of local recurrence on long-term follow-up. Conversely, 2D BT may result in excessive normal tissue toxicity in patients with smaller tumours [12, 13].

Due to advances in three-dimensional (3D) imaging techniques, the concept of image-guided BT (IGBT) has been developed in the last decades. In IGBT, magnetic resonance imaging (MRI) and/or computed tomography (CT) with the applicator in place is used for treatment planning [14, 15]. 3D treatment planning makes it possible to prescribe dose to a volume, rather than to a point. Furthermore, with the advance of techniques for image-guided adaptive BT (IGABT) it is possible to adapt the dose distribution to the anatomy of each patient during each fraction. The principle of IGABT is to apply repetitive 3D imaging (preferably with MRI) before EBRT and at time of BT, to take target volume regression and region of interest changes into account [16]. The objective of dose optimisation in cervical cancer BT is to achieve a high dose conformity, that is, a dose distribution that ensures adequate dose to the target volumes while minimising the dose to the OARs.

1.4. Regions of interest in cervical cancer brachythreapy

In 2005, the Gynaecological Working Group of the Groupe Européen de Curiethérapie of the European Society for Therapeutic Radiology and Oncology (GYN GEC-ESTRO) published recommendations on target contouring in 3D image-based treatment planning for BT for cervical cancer. They recommend definition of the gross tumour volume (GTV, Figure 1.2A-B), and high and intermediate-risk clinical target volumes (HR-CTV and IR-CTV, Figure 1.2C-D, respectively) [17].

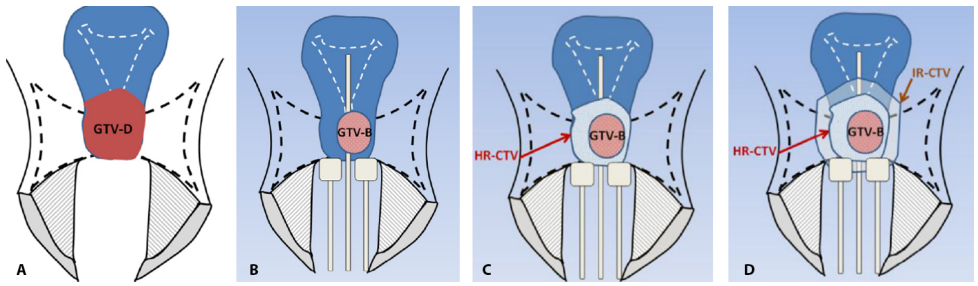


Figure 1.2: Abbreviations and definitions recommended by the GEC-ESTRO: coronal diagrams of an inserted tandem-ovoid applicator; (a) gross tumour volume at time of diagnosis (GTV-D); (b) gross tumour volume at time of BT (GTV-B); (c) high-risk clinical target volume (HR-CTV); (d) intermediate-risk clinical target volume (IR-CTV). Adapted from [14].

1.5. Dose-volume concepts in brachytherapy

The typical heterogeneity of the BT absorbed-dose distribution complicates dose prescription and reporting. Cumulative dose volume histograms (DVH) are recommended for evaluation of the complex dose heterogeneity. A DVH provides information about the volume irradiated as function of absorbed dose [18]. DVH parameters for GTV, HR-CTV, and IR-CTV that are recommended for reporting by the GYN GEC-ESTRO are the minimum dose delivered to 90 and 100% of the respective volume D_{90}, D_{100}, respectively. For OARs, the minimum dose in the most irradiated 0.1, 1 and 2 cc tissue volume are recommended to report ($D_{0.1cc}$, D_{1cc}, and D_{2cc}, respectively) [19].

BT is not delivered to the patient in one continuous irradiation but is divided into fractions. Currently in BT, the dose is delivered at either at a continuous low-dose rate (LDR, typically 0.5 Gy/h to the HR-CTV), pulsed-dose rate (PDR, typically 0.5 Gy/h to 1 Gy/h) or in a few large high-dose-rate (HDR, ~7 Gy) fractions. In HDR BT the irradiation is typically delivered over three to five fractions.

The combined total dose from EBRT and BT can be calculated using a linear quadratic model to determine the equivalent dose in 2 Gy fractions (EQD2), which enables dose addition. The American Brachytherapy Society (ABS) and the GYN GEC-ESTRO recommend a combined (EBRT + BT) D_{90} dose for the HR-CTV of 80-90 Gy EQD2. In addition, the ABS recommends dose limits for the bladder, rectum, and sigmoid D_{2cc} of ≤90 Gy, ≤75 Gy, and ≤75 Gy EQD2, respectively [20, 21].

Figure 1.3 shows the isodose distribution of a patient with distal right parametrium and upper third vaginal involvement at BT, treated with an IC/IS applicator using parallel and oblique needles. Illustration A shows the IC standard loading dose distribution which was used as starting point in the dose optimisation. Incomplete coverage of the target volume (shaded dark red region) with the 100% isodose (red contour), accompanied by excessive dose to the bladder and rectum can be seen. Illustration B shows the IC/IS optimised final dose distribution where IS needles are added. The needles were gradually loaded while simultaneously the dwell times in the tandem and applicator were manually adjusted to achieve near-complete coverage of the HR-CTV with the 100% isodose whilst meeting dose constraints of bladder and rectum. [8].

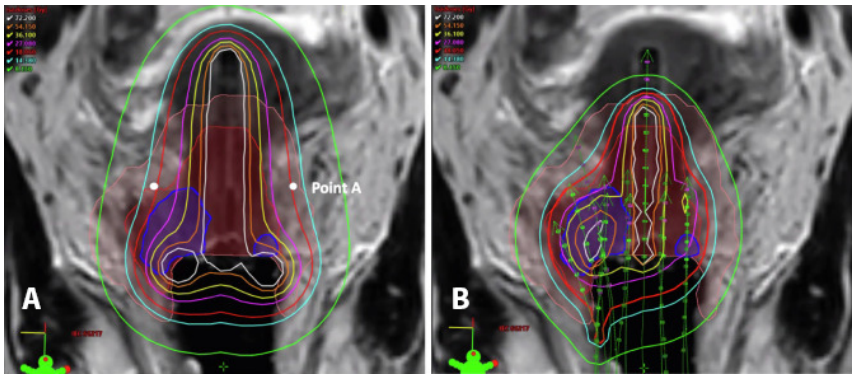


Figure 1.3: Dose distribution examples of a patient with distal right parametrium and upper third vaginal involvement; (a) dose distribution using an IC applicator only, resulting in the standard pear-shaped dose distribution; (b) dose distribution using additional IS needles, resulting in an optimised dose distribution. Adapted from [8].

1.6. Workflow brachytherapy

The treatment procedure of BT is a multi-step process including applicator implantation, imaging, treatment planning, treatment delivery, and applicator removal. The procedure begins with placing the applicator in the patient. CT and/or MRI scans are taken for verification of the position of the applicator and for delineation of the target regions and OARs. The images are sent to the treatment planning system. Calculation of absorbed dose to anatomical structures requires that the geometry of the applicator with its source dwell positions is defined within the patients' image data set. Therefore, the applicator is reconstructed on the images and the target volumes and OARs are delineated according to the GYN-ESTRO GYN working group recommendations [17]. Figure 1.4A shows an example of such structure delineation on MRI image and Figure 1.4B shows the 3D visualisation.

Based on the GYN GEC-ESTRO and the ABS recommended dose limits for the target and the OARs, a treatment plan in generated and optimised. The radiation oncologist has to check and approve the treatment plan before it can be delivered to the patient. If approved, the afterloader is coupled to the needles and the applicator, the radioactive source is driven out of the afterloader and the treatment plan is delivered. When the irradiation is completed, the needles and applicator are uncoupled from the afterloader and removed from the patient. The patient may be discharged the same day.

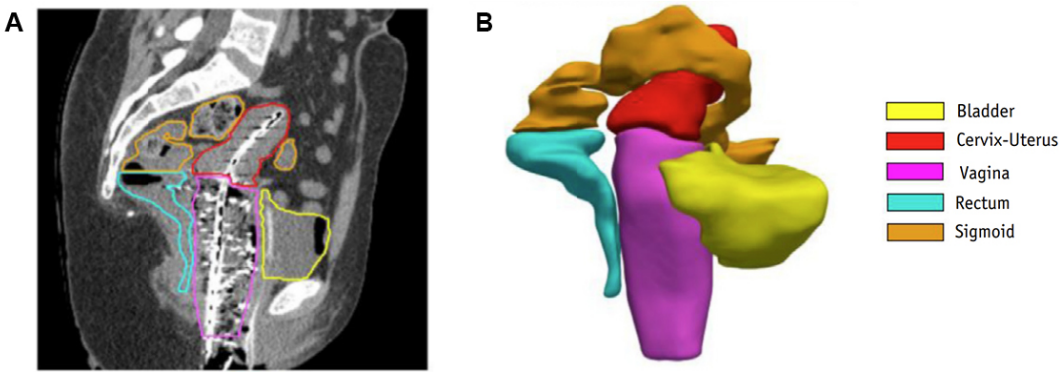


Figure 1.4: Example of structure delineation on MR image; (a) sagittal view; (b) corresponding 3D-structures. Adapted from [22].

1.7. Standard applicators

A wide variety of commercially available applicators exists for IC BT. Classic IC applicators consist of a tandem, and a structure placed against the vaginal fornices, such as a ring (T&R), a pair of ovoids (T&O) or a cylinder (Figure 1.5A-C respectively). The split-ring applicator (Figure 1.5D), w is a more modern applicator containing a tandem and two half rings. Based on the length and curvature of the uterine cavity of the patient, an appropriate length and angle of the tandem are selected. The (split-)

ring, ovoids, and cylinder are available in different sizes. To ensure the best dose differential between the tumour and normal tissue, it is important to select the largest ovoids/rings that can fit in the fornices [5].

These commercially available IC applicators are limited in their flexibility due to being one-size-fits-all products with fixed dwell positions. The capacity to extend the dose distribution through IS needles is constrained by their fixed positions and angles. Only which fixed needle positions are going to be used and the insertion depth of the needles can be adjusted manually. As a consequence, radioactive source placement may be suboptimal for advanced cancer or in other challenging patient cases and the treatment plan may be suboptimal (see Figure 1.3A).

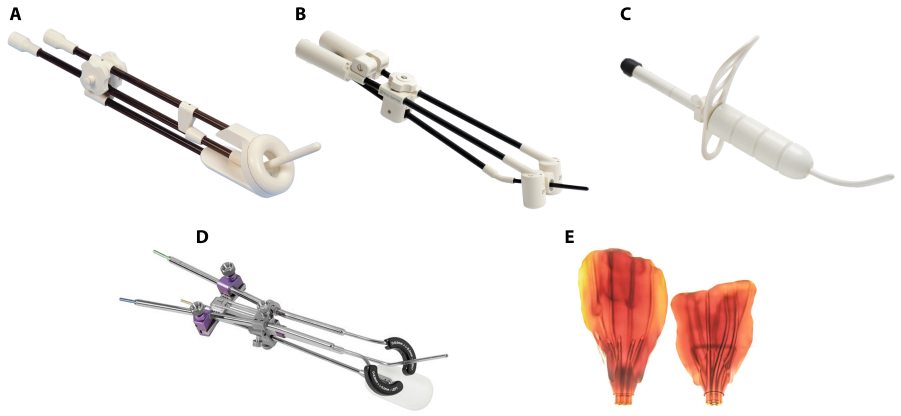


Figure 1.5: Overview of different applicator types; (a) tandem and ring applicator; (b) tandem and ovoid applicator; (c) tandem and vaginal cylinder applicator; (d) tandem and split-ring applicator; (e) 3D-printed ARCHITECT applicator of two different patients with curved internal needle channel. Adapted from [23, 24].

1.8. Personalised applicators

The aim to optimise treatment conformity in patients with challenging anatomies has led to the development of patient-tailored applicators, which are fabricated through 3D-printing techniques. 3D-printers are used to produce customised applicators or some parts of applicators to be assembled with commercially available applicators. An example of such an applicator is the first conceptual design of the ARCHITECT-applicator (Figure 1.5E) [24]. The ARCHITECT-applicator is a concept 3D-printed patient-tailored applicator including multi-curved needle channels for both IC and guided IS use. The outer shape of the ARCHITECT-applicator is derived from the vaginal anatomy.

1.9. Project goal

The goal of this project was to develop and validate a complete and feasible embodiment design for a 3D-printed HDR BT applicator with a custom vaginal topography and curved channels for needle guidance, based on the patient's anatomy and tumour location. This was achieved by performing multiple analyses leading to a comprehensive list of design requirements for the personalised applicator, developing conceptual designs, prototyping and refining these conceptual designs into final designs and validation of these final designs. For the validation of the final designs, a user experience experiment was carried out involving three radiation oncologists from Erasmus MC. Moreover, a dosimetry experiment was conducted to validate the suitability of PA-12 as a material for the applicator.

1.10. Scope of the project

This project focuses on development of a 3D-printed HDR BT applicator for the treatment of LACC. The geometry of the applicator will be based on a 3D-model of the patient's vaginal cavity, obtained from CT/MRI images. The guidelines for delineating the vaginal cavity on CT/MRI images to create this vaginal cavity 3D-model fall outside the scope of this project. The applicator incorporates personalised curved needle channels generated according to the tumour's location and the patient's anatomy. The software that generates these personalised needle channels also is not within the scope of this project.

2

Project approach

2.1. Project partners

Besides involvement of Delft University of Technology, this project is done in collaboration with multiple parties. A short description of the parties and their involvement in the project will be given below.

Erasmus MC: The Department of Radiotherapy within the Erasmus MC provided the patient data for the design of the applicator. Throughout the project, multiple meetings with experts in the field of BT and radiotherapy were held for input and feedback on the analyses, conceptual designs and validation experiments. In addition, the validation experiments have been taken place at Erasmus MC and are done with equipment of Erasmus MC.

Elekta: Elekta develops and produces radiation therapy and radiosurgery-related equipment and clinical management for the treatment of cancer. Elekta is the global market leader in BT devices, these include the Flexitron afterloader, the Geneva and Venezia applicator and the Oncentra Brachy treatment planning software. Throughout the project, Elekta provided the Geneva applicator, the Geneva applicator manual, multiple ovoid guiding tubes and multiple flexible implant tubes.

Oceanz: Oceanz is a 3D printing company which facilitates ISO9001 and ISO13485 certified production environments, including biocampatible 3D printing material. During this project, Oceanz provided the manufacturing of the conceptual designs and the parts used for the validation experiments.

2.2. Design process

To be able to develop a complete and feasible embodiment design for the new applicator, the basic design cycle described by Roozenburg and Eekels is used (Figure 2.1) [25]. This model represents the five fundamental reasoning steps in the process of designing: analysis, synthesis, simulation, evaluation and decision.

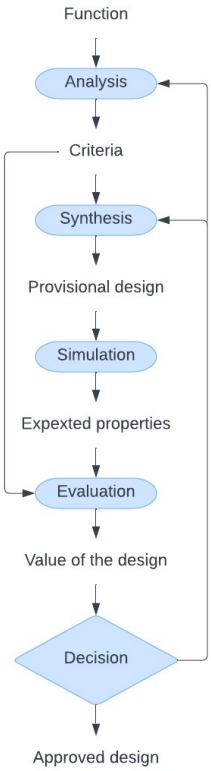


Figure 2.1: The phases of the Basic Design Cycle by Roozenburg and Eekels [25].

The following short descriptions of each phase are obtained from the Delft Design Guide [26]:

Analysis: The aspects related to the design goal or design problem are examined. Analytical reasoning yields information that informs the design criteria and eventually the requirements.

Synthesis: Possible solutions are generated. Synthesis yields (elements of) design proposals that potentially offer valuable (parts of) solutions to the problem.

Simulation: Representations of (elements of) design proposals are generated. This can be done with images, a digital representation or a physical representation. Simulation yields representation with which their potential value can be evaluated.

Evaluation: The potential value of the design proposals are reasoned through their simulated representation. This happens in relation to the design criteria. Evaluation produces an understanding of the current value of (an element of) the design proposal and informs design making.

Decision: The relative value of (an element of) the design proposal are reasoned and there is decided hot to proceed. Decision making informs the next cycles of design: whether to repeat a cycle, proceed (to an element of) the design proposal, or focus on other elements instead.

2.3. Structure of report

This report is structured following the five fundamental reasoning steps from the Basic Design Cycle. Chapter 3 presents the analyses that are done and has as output the list of requirements/criteria for the design of the personalised applicator. Subsequent, Chapter 4 describes the conceptual designs generation (synthesis phase) and has as outcome two concept designs. Chapter 5, is about the prototyping process and how the final design of the applicator was developed (simulation phase). These final designs are evaluated to check whether they meet the established requirements, which will be addressed in Chapter 6. In Chapter 7, some discussion points will be elaborated and some recommendations for future designs will be listed. A conclusion will be given in the final Chapter 8 (decision phase).

3

Analysis

To achieve a better understanding of the design values, requirements and wishes for the new applicator design, an analysis phase is required. The following analyses were done: a literature analysis (prior to the project), field research, a state-of-the-art applicator type analysis, an applicator parts analysis, a process tree analysis and a risk analysis. The information gathered from these analyses led up to the list of requirements for the new applicator design.

3.1. Literature analysis

Prior to this project, a literature study was completed. One of the study aims was to evaluate the relation between the geometry of different IC and hybrid applicator types in HDR BT. The study included 39 scientific articles from which dose-volume histogram parameters were extracted for the HR-CTV and OARs. From the 39 included articles, the HR-CTV D_{90} and the OARs D_{2cc} values were extracted. The differences between these values and the planning aims (desired dose) were analysed. Comparisons were made between applicator geometries and addition of IS needles, see Appendix A. The outcomes of this literature study appeared to indicate that an IC ring structure may have advantages in terms of dose distribution. Hence, it is preferable for the personalised applicator design to potentially incorporate an IC ring structure.

3.2. Field research

A month prior the start of the thesis project, the student had the opportunity to observe the treatment procedure at Erasmus MC. The placement of the applicator and IS needles in two different patients was witnessed in the operating room. Following, the acquisition of MRI scans for the patients, the delineation of the target structures and OAR on the MRI scans, as well as treatment planning conducted by the radiotherapy technologists was observed. Lastly, treatment delivery was observed. This experience provided the student with valuable insights into the tasks performed by the radiotherapy technologists, the treatment workflow and applicator usage.

3.3. State-of-the-art applicator types analysis

To understand the current state of the market of BT applicators for cervical cancer and their working principles and limitations, a state-of-the-art applicator types analysis have been conducted. Six standard applicator types and eight experimental applicator types (cervical BT and vaginal BT) are included in this analysis, see Appendix B. Table 3.1 and Table 3.2 list the gathered information of the standard applicator types and the experimental applicator types, respectively. The information of the standard applicator types is obtained from multiple user manuals, while information of the experimental applicator types is obtained from scientific articles found online. Regarding the standard applicator types, the gathered information shows that the tandem of the Geneva applicator is available in the most angles and lengths. Regarding the experimental applicators, the information indicates that there is one experimental 3D-printed applicator that contains personalised IS needle channels based on the tumour location and of which the geometry is based on the patient's vaginal cavity: the DMBT tandem with 3D printed template applicator [27].

Table 3.1: Analysis of 6 different standard applicator types.

Standard applicators								
Name of applicator	**Intended use**	**IC/IS options**	**Guided IS needle options**	**Tandem sizes and angles**	**Ring/ovoid sizes and angles**	**Max number of needles**	**Cervical stopper**	**Additional options**
Geneva [28]	Cervix, Endometrium	IC, IC/IS	Parallel to the tandem	l = 30-80 mm, 15, 30 and 45°	13-40 mm	Smallest ovoids: 6 Largest ovoids: 14	Yes	Rectal retractor
Utrecht [29]	Cervix, Endometrium	IC, IC/IS	Parallel to the tandem	d = 4 and 6 mm 15, 30 and 45°	15, 20, 25 and 30 mm 15, and 25°	14	Yes	Rectal retractor
Venezia [30]	Cervix, Endometrium	IC, IC/IS	Parallel and oblique to the tandem	l = 30-70 mm 15 and 30°	22, 26 and 30 mm 60°	Smallest ring: 12 Largest ring: 16	Yes	Perineal template
Vienna ring [29]	Cervix, Endometrium	IC, IC/IS	Parallel to the tandem	d = 4 and 6 mm 60°	26, 30 and 34 mm 60°	Smallest ring: 7 Largest ring: 9	No	Rectal retractor
Vaginal CT/MR Multi channel [29]	Vagina, Cervix, Endometrium	IC	No	l = 40 mm 15° l = 60 mm 30° l = 80 mm 45°	d = 25, 30 and 35 mm	Smallest diameter: 6 Largest diameter: 8	No	Perineal template
Vaginal CT/MR [29]	Vagina, Cervix, Endometrium, Rectum	IC	No	l = 40 mm 15° l = 60 mm 30° l = 80 mm 45°	d = 20, 25, 30 and 35 mm	N/A	No	Perineal template

Table 3.2: Analysis of 8 different experimental applicator types.

Experimental applicators					
Name of applicator	**Intended use**	**IC/IS options**	**Guided IS needle options**	**Intrauterine tube**	**Notes**
Capri applicator [31]	Cervix, Endometrium, Rectum	IC	No	No	- No guided IS needle option; - Needle channels cannot be adapted to the location of the tumour/OARs; - The flexible, inflatable device conforms to the patient's tissue, reducing air gaps and stabilizing the applicator position; - Applicator contains 13 IC channels.
Vaginal mold [32]	Vagina, Cervix	IC	No	No	- Time consuming procedure to develop the final vaginal mold applicator; - No guided IS needle option; - Material not sufficiently water equivalent; - The appearance of the applicator and the dose distribution can be customized to provide an optimal treatment for each patient; - Catheters placed by hand in applicator.
3D printed vaginal template [33]	Cervix, Endometrium	IC, IC/IS	Parallel and oblique to the uterine tube (up to 35°)	Yes	- Intracavitary ring source channel is replaced by multiple needles, resulting in the use of many needles; - Up to 15 needles can be inserted; - Steering holes in the printed templates can be individualised; - Not mentioned how the applicator is stabilised in patient.
Tulip [34]	Vagina, Cervix, Parametrium	IC/IS	Parallel and oblique to the uterine tube	Yes	- Needs a needle insertion guidance add-on at the proximal end of the applicator and a needle template add-on at the distal end of the applicator, but there is no needle guidance between these two parts; - 8-16 IS needles; - 3D-printed personalised (curved needle channels) add-on for standard applicator types; - The IS needles can be put parallel to the tandem as well as oblique at desired angles.
TARGIT [35]	Cervix, Endometrium	IS	Parallel and oblique to the uterine tube	Yes	- Only for T&O applicators; - Not mentioned how the needles are fixated/locked; - Template can guide up to 4-6 needles; - 3D-printed template designed to attach to tandem of T&O applicator and to guide IS needles.
Customised vaginal mold [36]	Vagina, Cervix	IC	No	No	- All needle channels are situated in the mid-coronal plane of the applicator; - 3D-printed (stereolithography, SLA) applicator based on 3D- model of the vaginal cavity; - Customised needle channels; - Applicator designed in 2 pieces to be able to be inserted in the anatomical limitation of a 2.5 cm narrow vaginal introitus; - The pieces are assembled using a stainless-steel plate.
Balloon-sleeve applicator [37]	Vagina, Endometrium	IC	No	No	- No guided IS needle option; - Balloon fills the vaginal fornices, which may be able to conform better to deep vaginal fornices; - Applicator can maximally obtain 5 IC channels; - Balloon gets inflated with 40 cm3 of water; - Inflatable balloon sleeve is placed over a standard cylinder applicator.
DMBT tandem with 3D printed template [27]	Cervix, Endometrium	IC, IC/IS	Angle and location of needle channel based on patient and tumour geometry	Yes, a straight DMBT tandem	- Applicator consist of one piece, it does not become clear how the applicator is inserted; - A patient-specific 3D-printed vaginal template with built-in needle tracks; - 3D-printed vaginal template based on vaginal cavity of patient; - The number of needles and their geometric positions are manually optimised based on patient anatomy.

3.4. Applicator parts analysis

To identify and understand the functions that the personalised applicator must be able to perform, a function analysis of the different parts of the Geneva and Venezia applicators (Elekta Brachytherapy, Veenendaal, the Netherlands) is performed. These two applicators were chosen for the analysis because they are the state-of-the-art ovoid and ring applicators produced by Elekta. Examining the functions of the applicator parts can make it easier to understand the interactions between the various parts of the applicators and can help identifying areas where improvements can be made. In addition, the function analysis can be used to prioritise design decisions and ensure that most important functions are adequately addressed. Figure 3.1 and Table 3.3 [30, 28] show the functions of the applicator parts, which were identified using the user manuals of the applicators.

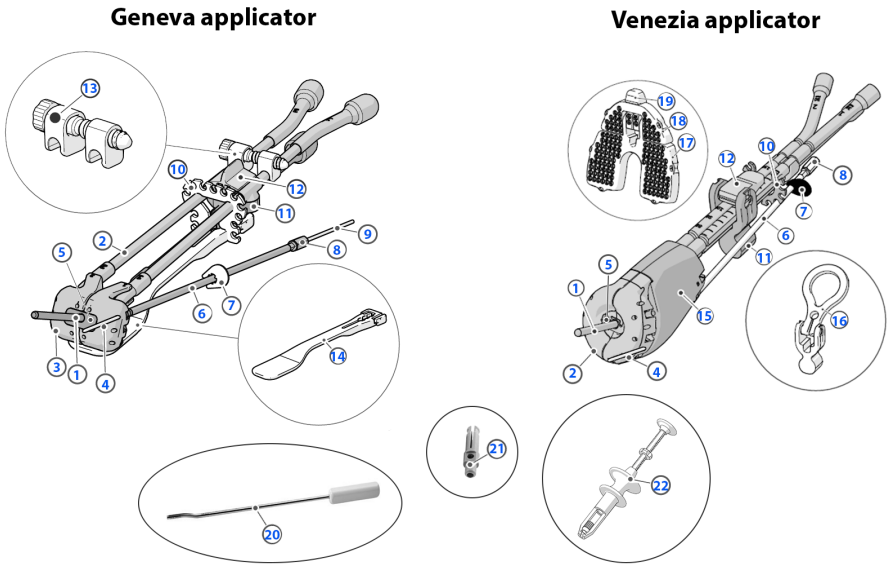


Figure 3.1: The parts of the Geneva and Venezia applicators and their associated tools. Adapted from [30, 28]

Table 3.3: The functions of the various parts and tools of the Geneva and Venezia applicators. The first column corresponds to the corresponding part number in Figure 3.1. The second column lists the names of the parts, and the third column lists the function of each part. Adapted from [30, 28].

No.	Part name	Function
1	Intrauterine tube/tandem	To guide the radioactive source through to a certain position (dwell position)
2	Ring/ovoid tubes	To guide the radioactive source through to a certain position (dwell position)
3	Ovoid pair	To attach the guiding tubes (5) and to guide the needles (4)
4	Interstitial needle	To guide the radioactive source of the afterloader to the target volume
5	Cervical stopper	To limit the depth of insertion of the tandem (1)
6	Guiding tube	To insert and guide a needle (4)
7	Number tag for guiding tube (6)	To identify the needle/channel number
8	Nut	To lock the needle (4) in place
9	Obturator	To support the needle (4) during insertion and to prevent kinking or breaking of the needle
10	Bracelet for guiding tube (6)	To sort the interstitial needles (4)
11	Fixation element	To fixate the ring/ovoid tubes (2) (prevent from detaching when assembled)
12	Fixation clip	To fixate the fixation element (11)
13	Spreading clip	To move the ovoid tube (2) laterally
14	Rectal retractor	To distance the rectum from the applicator

Continued on next page

15	Vaginal cap	To insert and guide the needles (4) and to treat tumour tissue in the upper two thirds of the vagina
16	Perineal bar	To fixate the applicator to the patient
17	Perineal template dorsal	To insert needles (4) parallel from the perineum into the parametrium
18	Perineal template ventral	To insert needles (4) parallel from the perineum into the parametrium
19	Interstitial lever	To hold the perineal template dorsal (17) and perineal template ventral (18) together
20	Needle lock tool	To turn the needle lock pins (21) to lock them into a perineal template (17, 18)
21	Needle lock pins	To lock the needles (4) into a perineal template (17, 18)
22	Needle insertion tool	To insert the needles (4) into the tissue of the patient with a preferred depth

The tandems of the Geneva and the Venezia applicator are shown in Figure 3.2A-B, respectively. Regarding the cervical stopper and dead space in the tip of the tandem, there are some differences. The cervical stopper of the Geneva applicator has a rectangular shape, while the cervical stopper of the Venezia applicator features two notches at the top. This likely will make it more difficult to design a connection to the cervical stopper of the Venezia applicator in comparison to the cervical stopper of the Geneva applicator The lower row in Figure 3.2 displays the tandem tips of both applicators. The distance between point 1 and 3 indicates the dead space in the tip (the distance between the outer tip of the tandem and the most distal dwell position). In the Geneva applicator, this distance is 8.3mm, compared to 12mm in the Venezia applicator [28, 30]. Due to these stated differences, the tandem of the Geneva applicator was chosen for use in the design of the personalised applicator

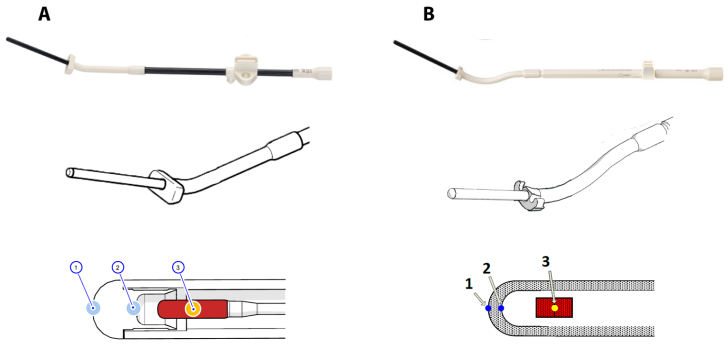


Figure 3.2: Comparison between the tandem and cervical stopper of the Geneva and the Venezia applicator; (a) Geneva applicator; (b) Venezia applicator. Images not on scale. Adapted from [29, 30]

3.5. Process tree analysis

Between its origination and disposal, the new applicator will go through different processes. Each of these processes comes with certain requirements and wishes for the new applicator design. In order to identify these requirements and wishes, a list of processes that the new applicator is expected to undergo is created and compared with the workflow of a currently used applicator at Erasmus MC, see Figure 3.3. To get the most complete overview possible, this is done in corporation with a PhD student from Erasmus MC who is involved in the workflow of the applicator. The comprehensive process tree, with the individual steps per process, can be seen in Appendix C.

As can be seen in Figure 3.3, there will be some additional processes in the workflow of the new applicator. On the images obtained during the first BT fraction, not only the target volumes and the OARs will have to be segmented in the Medical Image Merge (MIM) software, but also the vaginal cavity will need to be segmented. This is necessary to be able to create the 3D-model of the patient's vaginal cavity hence to make the patient-specific applicator. In addition, the steps applicator modelling, trajectory plan-

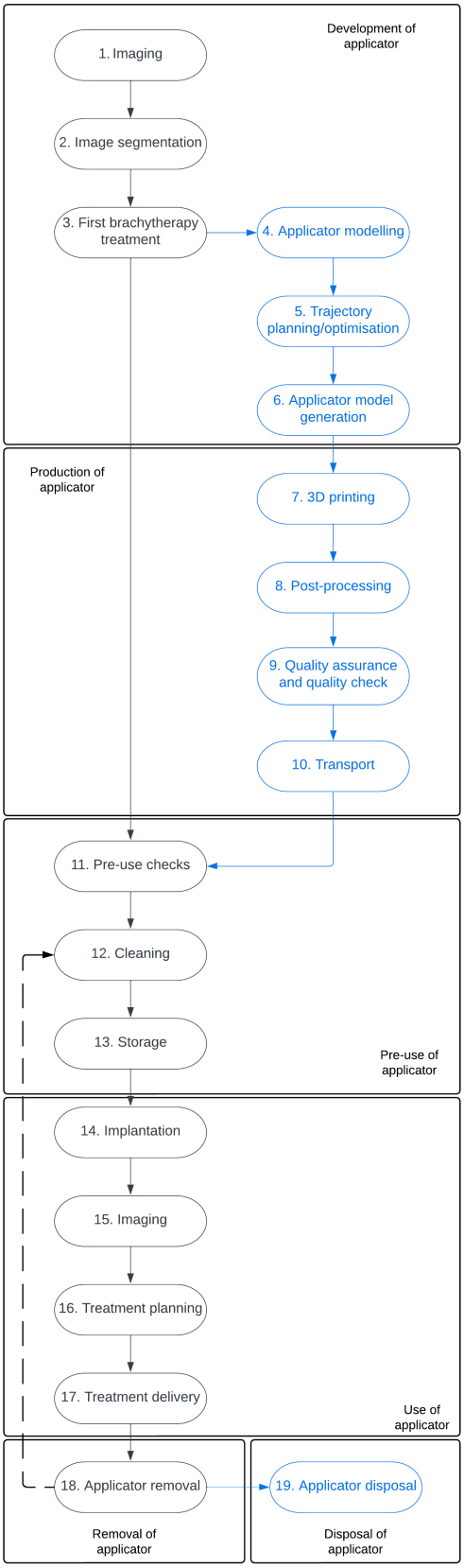


Figure 3.3: Processes in the applicator workflow. Black processes are of the applicator currently used in the clinic at Erasmus MC, blue are the additional processes for the new applicator. The boxes represent the workflow phases.

ning and applicator model generation, will be new partially automated processes in the workflow. The step applicator reconstruction will also be different from current applicators because the needles will no longer be at a fixed position and angle. The new steps 3D-printing, post-processing, quality assurance check and packing and transport will be performed by the 3D-printing company Oceanz. Opposed to a currently used applicator, the new applicator will be a single-use device and therefore will be disposed after the treatment.

3.6. Risk analysis

The European Medical Device Regulation 2017/745 (MDR) are a set of laws and guidelines that govern the manufacture, distribution, and marketing of medical devices within the European Union [38]. The MDR also covers clinical investigations conducted in the EU in which non-CE-marked medical devices are used. If there is an intention to conduct medical trials with the medical device, MDR compliance should be considered to facilitate transitions from pre-clinical to clinical research. All medical devices must comply with all relevant obligations of the MDR. However, some requirements depend on the device classification. According to the guidelines in Articles 2 and 51, and Annex VIII of the MDR 2017/745 the new applicator is considered a 'single-use', 'short-term' medical devices that is not 'surgically invasive' but 'invasive with respect to body orifices', and thus may be considered as a class IIa device (Rule 7, Annex VIII).

The MDR applies to medical devices that are intended to be placed on the market and made available for commercial use. On the other hand, an Investigational Medical Medical Device Dossier (IMDD) is required when you want to conduct clinical investigations or studies in the Netherlands using the medical device on human subjects before commercialising it (in accordance with Annex XV Article 2.2 of the MDR). The IMDD is similar to technical documentation required by the MDR (Annex II), and therefore requires a risk analysis (Annex II Article 5). The risk analysis helps identify potential hazards, assess their severity, and determine the likelihood of occurrence during the clinical investigation.

As concluded from the process tree analysis, the new applicator will require several new steps and processes. In order to ensure safety, reliability and quality of the new applicator, the potential hazards and risks of the steps of the process tree must be determined. To help identify the potential hazards, asses their severity, and determine the likelihood of occurrence, a risk analysis following International Organization for Standardization (ISO) 14971:2019 and ISO/TR 24971:2020 is conducted [39, 40]:

1. A risk analysis:
    - Description of the intended use of the medical device and reasonably foreseeable misuse;
    - Identification of hazards and hazardous situations associated with the medical device;
    - Estimation of risks for each hazardous situation.
2. A risk evaluation analysis;
3. A risk control analysis;
4. Production and post-production activities analysis.

For the first step of the risk analysis, the intended use and reasonably foreseeable misuse from process step 10 (transport to Erasmus MC) to the last process step 19 (applicator disposal) were identified. Following ISO 1497:2019 paragraph 3.6, 'intended use' is the use for which a product, process, or service is intended according to the specifications, instructions and information provided by the manufacturer [39]. In addition, following paragraph 3.15, 'misuse' is defined as the use of a product or system in a way not intended by the manufacturer, but which can result from readily predictable human behaviour. A meeting with two radiotherapy technologists, one medical physicist, two PhD researchers, and one postdoctoral researcher was held at Erasmus MC for input and feedback. In order to obtain the most complete overview possible, the intended use and reasonably foreseeable misuse of the preceding 'development of applicator' phase (step 1 to 6), are identified by the PhD researcher who is involved in the path planning software development.

For each identified misuse, the level of misuse was determined. The four different levels of misuse were use (US: using the device for a non-intended purpose, patient, application, environment, etc.), user (UR:

use by a non-intended user), process of use (PU: within the intended use and by the intended used, but with wrong steps/actions/decisions) and involved equipment (EQ: with non-intended or incompatible accessories/aids/other devices/resources/materials etc.). In addition, the foreseeable sequence of events of the misuses were identified. This included identifying the potential outcomes of the misuses and possible issues that could arise during the intended use. With this information, the hazards and hazardous situation were identified. The complete risk analysis table can be seen in Appendix D.

3.6.1. Risk evaluation

To ensure the safety of the new applicator, a risk evaluation is conducted. For each identified hazardous situation the estimated risks are evaluated and it is determined if the risk is acceptable or not. According to paragraph 3.18 of ISO 1497:2019, the concept of risk has two key components: the probability of occurrence of harm and the consequences of that harm, that is, how severe it might be. Of every identified hazardous situation, the corresponding harms were identified. Values were assigned to the probability of occurrence and the severity of the harms (values 1-5, see Table 3.4). The qualitative description of the severity and probability values and the categorisation of the severity values are based on ISO/TR 24971:2020 and Poder et al. (2018) [40, 41]. The frequency of the probability is determined based on a 2-year timeframe, assuming 4 fractions per week, as recommended by the contributors. For comparison of probability of occurrence and severity values, articles were searched about risk analyses for HDR BT for cervical cancer. The identified risks are put in a 5x5 matrix for qualitative analysis, see Table 3.5. The risks associated with the numbers in the table can be found in Appendix D. The location in the table is based on the severity and occurrence scores of the risks.

Table 3.4: Severity and probability ranks and a qualitative description per rank. The frequency of the probability is determined based on a 2-year timeframe, assuming 4 fractions per week.

Severity		
Rank	**Qualitative**	**Categorization**
1	Negligible	Inconvenience, temporary discomfort.
2	Minor: minor dosimetric error	Suboptimal treatment plan. May result in temporary injury or impairment not requiring medical or surgical intervention.
3	Serious/major: potentially serious toxicity or tumour underdose	Wrong dose, dose distribution, location or volume. May result in injury or impairment requiring medical or surgical intervention.
4	Critical: possible very serious toxicity or tumour underdose	Very wrong dose, dose distribution, location, or volume. May result in permanent impairment.
5	Catastrophic/fatal	Results in death

Probability			
Rank	**Qualitative**	**Frequency**	**Percentage**
1	Failure unlikely	Less than once every two years	<0.2%
2	Relative few failure	Once every two years to once a year	0.2% - 0.5%
3	Occasional failure	Once a year to once every six months	0.5% - 1%
4	Repeated failure	Once every six months to once a month	1% - 6%
5	Failure very likely	More than once a month	>6%

Table 3.5: 5x5 Matrix for qualitative analysis of the identified risks. Green cells: insignificant or negligible risks; yellow cells: acceptable risks; orange cells: investigate further risk control options; red cells: unacceptable risks. The risks related to the numbers can be found in Appendix D.

Severity / Probability	Negligible 1	Minor 2	Major 3	Critical 4	Catastrophic 5
Failure very likely 5		R5, R14, R54, R56			
Repeated failure 4		R3, R4, R42, R49, R53	R45, R46		
Occasional failure 3		R7, R9, R15, R20, R36[42], R48, R52, R55, R62[42]	R8, R26, R37, R44, R50		
Relative few failure 2	R41	R1, R2, R6, R12, R16, R27, R29, R30, R31[42], R32, R47, R51, R61	R19, R21, R22, R28[43], R33, R35[42], R38[42], R57, R60		
Failure unlikely 1	R17, R18, R40	R10	R11, R13, R23, R24, R25, R39[42], R58, R59	R34, R43, R63	

3.6.2. Risk control options

For each identified risk, the current process control measure is determined and options to mitigate the risk are considered. Following ISO 1497:2019 paragraph 7.1, three different risk control options were considered: inherently safe design and manufacture, protective measures in the applicator itself or in the manufacturing process, and information for safety and, where appropriate, training to users of the applicator.

Risks to be addressed in the list of requirements

For the risks categorised in the red and orange cells of Table 3.5, further risk control options should be investigated. The six risks that are positioned in the orange cells of Table 3.5 are associated with the needle path planning software and because the project's scope are excluded from further analysis. Additionally, considering the project goal, only the risks that obtained the 'inherently safe design and manufacture' as risk control option were further analysed. These specific risks are listed in Table 3.6 and will be addressed within the list of requirements.

Table 3.6: Risks that are addressed in the list of requirements. Note: risks associated with the path planning software and risks that did not obtained 'inherently safe design and manufacture' as risk control option are excluded. The process step numbers in the second column refer to the process steps of the process tree of Appendix C.

Risk no.	Process step no.	Misuse description or foreseeable sequence of events of intended use
R19, R21, R22	12.1, 12.2, 12.3	Cleaning/disinfection/sterilisation of the applicator: applicator in not properly cleaned/disinfected/sterilised
R27	14.4	Determination of needle configuration (including depth): an extra needle needs to be inserted
R32	14.11	Implantation and assembly of the applicator to the tandem: applicator is not properly assembled to the tandem
R35	16.6	Reconstruction of the applicator and needles: applicator is incorrectly reconstructed
R60	14.13	Insertion of the needles to correct depth into the patient's tissue: needles are inserted with incorrect insertion depth
R61	14.14	Locking the needles by turning the nuts at the distal end of the guiding tubes: needles are not locked properly
R63	15.23	Imaging (MRI or CT scan): applicator material disturbs image

During a meeting with a radiotherapist-oncologist from Erasmus MC, it was mentioned that currently, the need for additional needle insertion during treatment is quite rare. Therefore, it was decided to not address risk R27 in the list of requirements.

3.7. List of requirements

The list of requirements for the new applicator design is listed in Table 3.7 and was established on basis of all gathered information in the previous listed analyses and using Pugh's checklist for generating design requirements [44]. The verbal forms used in the list of requirements conform to the usage described in Clause 7 of the ISO/IEC Directives, Part 2:2018 [45]: 'shall' indicates requirements and 'should' indicates recommendations. The reasoning for every requirement is stated in the third column of Table 3.7. The number(s) in this column refer to the corresponding process step or risk number(s).

Table 3.7: List of requirements for the new applicator. Second column: reason for the requirement; third column: corresponding process step and corresponding risk number(s).

Performance requirements (A)		
No.	**Requirement**	**Reason**
A.1	The applicator shall have the ability to guide 6F needles (obturater+catheter) (outside diameter: 1.9 mm) or flexible implant tubes (diameter: 0.9 mm)	To be able to guide the radioactive source to the target region (17.5)

Continued on next page

Table 3.7: List of requirements for the new applicator. Second column: reason for the requirement; third column: corresponding process step and corresponding risk number(s). (Continued)

A.2	The applicator shall have the ability to lock 6F needles	To ensure that the needles not displace during the treatment (14.9, 14.14, 14.17, 15.1, 15.5, 17.1, 17.5, R61)
A.3	The 3D-printed part(s) of the applicator shall facilitate the guidance of needles into the parametrium and upper vagina	To ensure proper target coverage for larger tumours (16.1, 16.3, 17.5)
A.4	The 3D-printed part(s) of the applicator shall not disassemble or break under a vertical and horizontal applied load of 15N to the distal end of the 3D-printed parts	To ensure that the 3D-printed parts do not break due to the force during insertion or removal of the applicator (14.11)
A.5	The 3D-printed part(s) of the applicator shall not deform or break when falling of a height of 2 meters	To ensure that the 3D-printed parts are not damaged and/or the channels are still accessible when the 3D-printed parts are dropped due to human error (14.3)
A.6	The applicator shall be able to produce a pear shaped isodose configuration	To obtain an isodose configuration conform traditional IC BT (16.3, 16.4, 16.5)
A.7	No uncured residues shall be left in the source channels after fabrication of the applicator	To ensure accessibility of the applicator channels and safety of the patient, and to ensure ability to clean/disinfect/sterilise the channels (12.1, 12.2, 12.3, 14.13, R19, R21, R22)
A.8	The applicator shall be able to be assembled to a Geneva tandem (Elekta Brachytherapy, Veenendaal, The Netherlands)	To deliver IC BT and for the stability when inserted (14.11, 16.3, R32)
A.9	When inserted in the applicator, the needles shall be able to be connected to the Flexitron afterloader	To deliver the radioactive source from the Flexitron afterloader to the target region (17.2, 17.5, 17.6)
A.10	The applicator shall be able to be immobilised within the vaginal cavity	To prevent displacement of the applicator during treatment (14.17, 15.1, 15.5, 17.1, 17.5)
A.11	The applicator should include a component to prevent channel mix-up	To reduce the risk of delivering the wrong dose due to channel mix up when the needles are inserted and/or when the guiding tubes are connected to the applicator (14.5, 14.6, 14.7)
Environment requirements (B)		
B.1	Performance of the 3D-printed parts (e.g. stiffness, strength) shall not noticeably be negatively affected inside temperature range of -20 °C to 60 °C and humidity of 90%	To ensure that transportation conditions do not affect the performance of the 3D-printed parts (10.1)
Life in service requirements (C)		
Size and weight requirements (D)		
D.1	The applicator parts shall be insertable through a P5 introitus (L-R width: 19 mm)	To ensure the insertion ability in the vaginal cavity (14.11)
D.2	The surface of the 3D-printed part(s) shall not cause any harm to the patient throughout the entire procedure	To prevent harming the users or patient during implantation and treatment (14.11)
Materials requirements (E)		

Continued on next page

Table 3.7: List of requirements for the new applicator. Second column: reason for the requirement; third column: corresponding process step and corresponding risk number(s). (Continued)

E.1	The material(s) of the applicator shall be MRI and CT compatible	To ensure safety when using imaging on the patient with the applicator inserted (15.3, R35, R63)
E.2	The material(s) of the 3D-printed parts shall not cause distortions or artefacts on MRI and CT scans	To ensure correct reconstruction of the applicator for treatment planning (15.3, 16.1, 16.2, 16.3, R35, R63)
E.3	The material(s) of the 3D-printed parts shall have similar dose attenuation properties as water	To ensure accordance with the TG-43 formalism for dose calculations (16.3, 16.4, 16.5)
Standards requirements (F)		
F.1	The material(s) of the 3D-printed parts shall be biocompatible per ISO 10993-1:2018	To ensure safety: the material of the applicator must not produce a toxic or immune response within the patient's body (14.1)
Ergonomics requirements (G)		
G.1	The outer shape of the assembled applicator shall conform to the vaginal cavity	To increase patient comfort, optimal needle channel planning and to ensure reliable placement of the applicator (14.11)
Safety requirements (H)		
H.1	The 3D-printed parts shall be able to be sterilized using an autoclave (134 °C, 3 minutes, 3.04 Bar) without being effected by the process	To ensure that the 3D-printed parts are able to be sterilised to ensure that the 3D-printed parts do not transmit infectious pathogens to the patient (12.2, 14.11, R22)
H.2	The design of the applicator shall ensure that the radioactive source can never come in contact with the patient material	To ensure patient safety (17.5)
Installation, operation requirements (I)		
I.1	The applicator shall be able to be assembled inside the vaginal cavity of the patient	To ensure that the applicator does not need to be assembled prior to insertion (14.11)
Wishes (J)		
J.1	The applicator should not need packing to be immobilised	For the comfort of the patient and the time of the implantation procedure
J.2	The applicator should contain an IC ring-structure	Result from the pre-done literature review

4

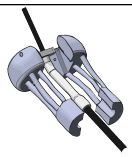
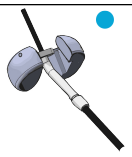
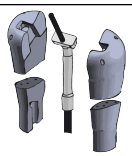
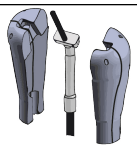
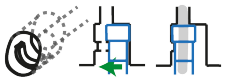
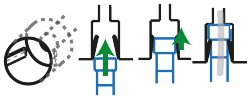
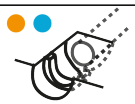
Conceptual designs

Once the requirements for the personalised applicator design had been formulated, the conceptual design generating phase began. In this phase, ideas and concepts of the new applicator design were generated.

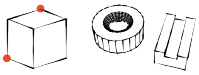
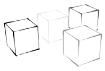
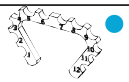
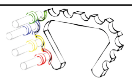
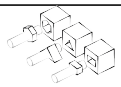
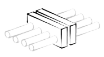
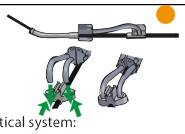
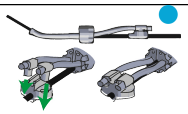
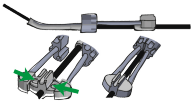
4.1. Concept generation

The conceptual design generation phase of the design process started with the initiation of idea generation. Based on the list of requirements (Table 3.7), the applicator design was broken down into multiple key aspects. These aspects were: the 3D-printed part(s) of the applicator, the needle locking mechanism, the visibility on MRI, the IC structure, preventing needle channel mix-up and the distal connection to the Geneva tandem. Subsequently, multiple 'how-to's' were generated, which can be found in E. During several brainstorming sessions, multiple potential solutions were gathered on these how-to questions, as shown in E. The morphological chart in Table 4.1 illustrates the various design alternatives generated for the different aspects using the solutions gathered from the 'how-to' questions. Additionally, the chart provides Various advantages and disadvantages associated with each solution.

Table 4.1: Morphological chart displaying design options per aspect gathered during brainstorming sessions. Orange dots indicate solutions implemented in Concept 1, while blue dots indicate solutions implemented in Concept 2.

3D-printed part(s)	 Wireframe: + reduced mass around source channels + printability - rigidity/stiffness - tissue can get in between channels	 Wireframe + shell: + reduced mass around source channels + printability - cleaning/sterilisation (edges and spaces)	 Top connected to ovoid tubes: + reduced mass + printability - small space for curved source channels	 Horizontal splitted parts: + reduced mass + printability - connection source channels - rigidity when assembled - ensuring source does not come into contact with patient	 Vertical splitted parts: + reduced mass + printability - space for source channels - rigidity when assembled - ensuring source does not come into contact with patient
Ovoid tubes connection/needle locking mechanism	 Slide system: Holes in 3D-printed parts to put proximal end of guiding tube in, sliding it sideways into an holder. + reversable connection + printibility - requires a lot of space	 Snap fit system: Holes with snap fit connection in 3D-printed parts to put proximal end of guiding tube in + requires less space than slide system - irreversable connection	 Current system: Holes in 3D-printed parts to put proximal end of guiding tube into an holder at the surface of the applicator. + reversable connection + printability + required space - limits the enty placement	 Needle lock pins: Insert needle in lock pin and place lock pin in template or other part to turn and lock the needle (currently used in prostate BT) + reversable connection + printability + does no need to be placed in entry region - required space	

Continued on next page

Visibility MRI	 Currently used MRI marker: Markers ae inserted in intrauterine tube and ovoids/ring. + easy to use - due to the diameter, it is not possible to place them in needle channels	 Reference points/structures in 3D-printed parts: - difficult to integrate and validate in the design	 Different materials: - all the different materials must be validated to check if they meet the requirements	 Cavities in 3D-printed parts filled with MRI marker fluid: - requires much space in 3D-printed part - ensurance that fluid will not leak
Intracavitary structure	 Flexible implant tube: - if with button: button must be integrated in the 3D-printed part - validation of placement in IC structure	 Intern IC guiding structure: - printability - cleanability/sterilisation	 Using current IC ring tube/structure: - requires lot of space in 3D-printed parts - no IC ovoid structure possible	 Using current IC ovoid tubes/structure: + MRI markers can be inserted - no IC ring structure possible
Preventing needle channel mix-up	 Currently used braclet: + easy to use - no numbering	 Color coded matching system: + easy to use - currently used 6F needles must be adjusted	 Bracelet with numbering: + easy to use + can be 3D-printed	 Bracelet with color coded system: - currently used 6F needles must be adjusted	 Shape lock: - currently used 6F needles must be adjusted
	 Currently used number tag: + easy to use - time consuming	 Color coded needle system: + easy to use - currently used 6F needles must be adjusted	 Integrate bracelet in 3D-printed parts: + easy to use - requires space in 3D-printed part	 Plug system: - unnecessary bending of needles	
Assembly to Geneva tandem: distal connection	 Vertical system: design system that can be 3D-printed and vertically assembled to the fixation element + easy to use in combination with insertion movement	 Currently used system: Snap-fit connection of Geneva ovoid tubes that is vertically inserted in the fixation element + easy to use in combination with insertion movement	 Horizontal system: design system that can be 3D-printed and horizontally assembled to the fixation element - horizontal movement can be difficult due to the insertion movement and space		

4.2. Concepts

Based on the advantages and disadvantages outlined in Table 4.1, two different design configurations were developed by combining design options from each row. The first concept is a combination of the orange dots in Table 4.1 and the second concept of the blue dots. These two different design concepts will be presented below.

4.2.1. Concept 1

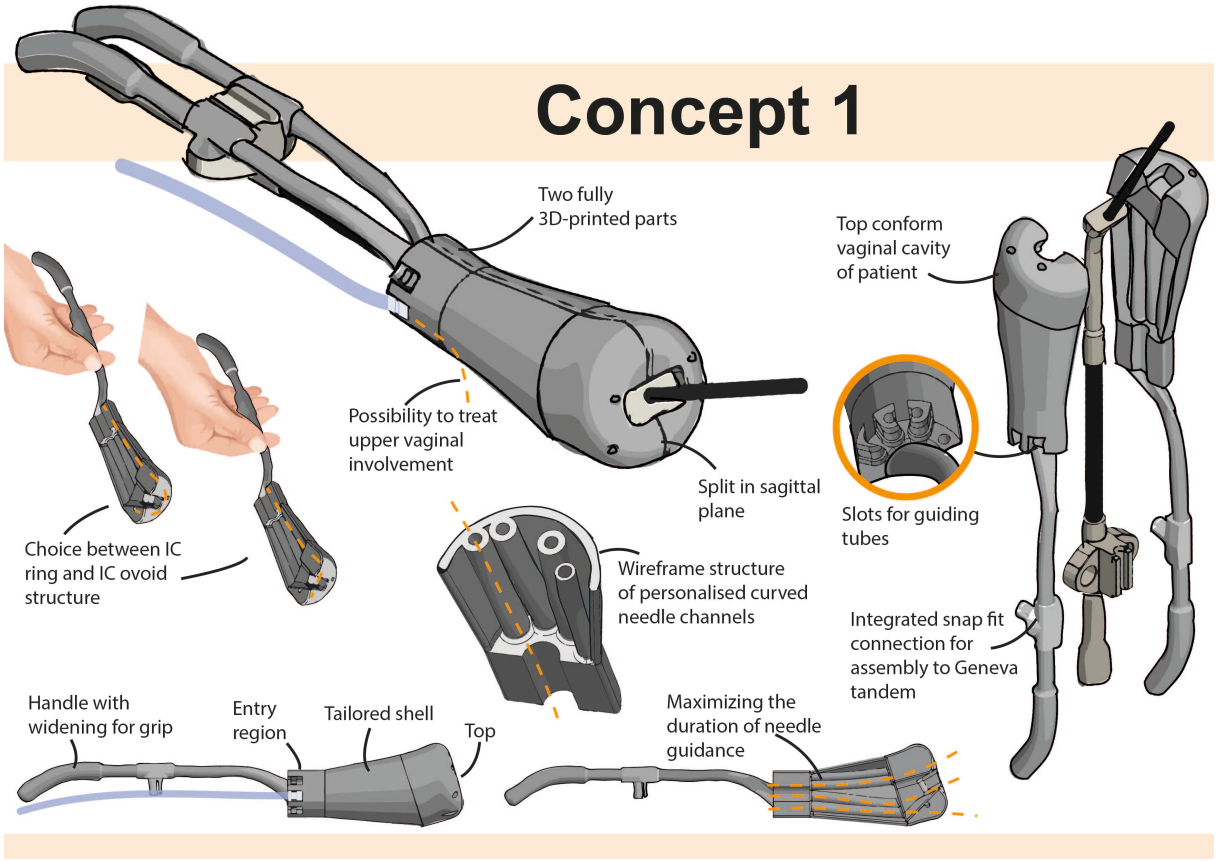


Figure 4.1: Concept 1 and its features: two fully 3D-printed parts, containing a tailored shell and a wireframe structure based on the personalised needle channels. The length of the parts makes it possible to treat upper vaginal involvement and facilitates maximum needle guidance. IS Needles can be inserted through guiding tubes which are clicked in the distal end of the 3D-printed parts. There can be chosen between an IC ring or ovoid structure.

Figure 4.1 presents Concept 1, which consists of two fully 3D-printed parts. These parts extend from just outside the introitus till the external os. Each part includes an entry region connected to a handle, a curved needle channel wireframe enclosed by a tailored shell, and a top conform the patients' vaginal cavity in which the cervical stopper is positioned.

Working principle Concept 1
Guiding tubes are placed in slots in the entry region of the 3D-printed parts. 6F ProGuide needles are inserted through the guiding tubes into the personalised needle channels. The 3D-printed parts can be held at the widening of the handle. After inserting the needle into the patients' tissue, the nut of the guiding tube is tightened to lock the needle in position. Users have the option to choose between an IC ring or IC ovoid structure. Additionally, the 3D-printed parts can be assembled to the Geneva tandem using the integrated snap-fit mechanism.

Key aspects Concept 1

- **3D-printed parts**: the 3D-printed parts reach from just outside the introitus till the external os. Due to the length of the prints, it is possible to treat upper vaginal involvement. In addition, IS needles are guided from outside the introitus to the tissue, which reduces the potential for needle displacement. By implementing a wireframe structure, mass around the needle channels is removed, thereby enhancing the printability of the channels. The shell adds rigidity to the applicator and prevents tissue from getting in between the wireframe;
- **Needle locking mechanism**: the needles are locked in position using the nuts of the guiding tubes;
- **Visibility MRI**: one MRI marker can be placed in the Geneva tandem;
- **Intracavitary structure**: the user can choose to integrate either an IC ring or ovoid structure. A flexible implant tube or a needle catheter will be inserted into the IC structure to guide the source;

- **Preventing needle channel mix-up**: the entry region of the 3D-printed parts extends just outside the introitus, which makes it possible to observe from outside the patient in which needle channel the needles are placed. If necessary, the currently used bracelet can be added to separate the guiding tubes;
- **Assembly to Geneva tandem**: the handles of the 3D-printed parts feature a snap-fit element that is based on the snap-fit mechanism of the Geneva ovoid tubes. Therefore, the 3D-printed parts can be clicked in the fixation element of the Geneva tandem.

4.2.2. Concept 2

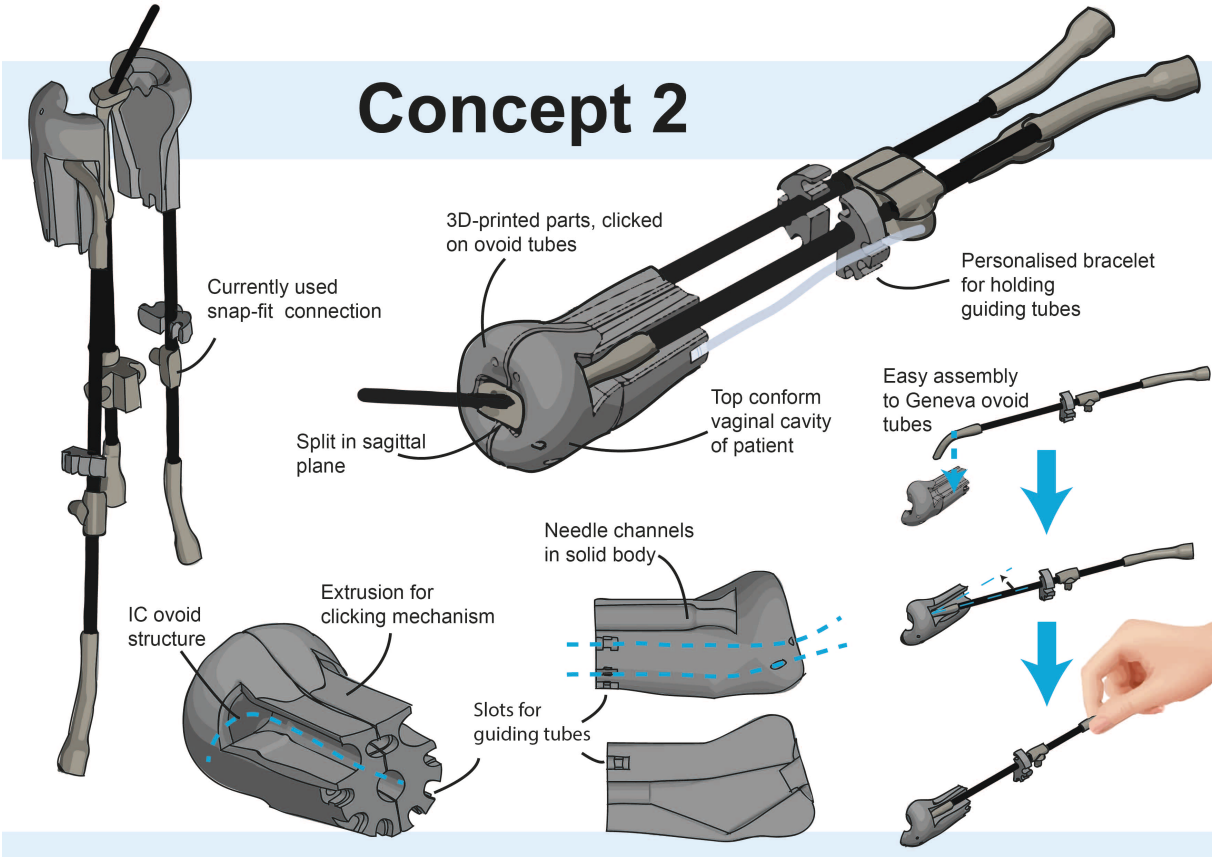


Figure 4.2: Concept 2 and its features: two short 3D-printed parts to ensure printability of the needle channels. The parts can be clicked on the Geneva ovoid tubes, which provide the IC structure. IS needles can be inserted through guiding tubes which are clicked in the distal end of the 3D-printed parts. To prevent needle channel mix-up, a customised 3D-printed bracelet can be clicked on the ovoid tubes to separate the guiding tubes.

Figure 4.2 presents Concept 2, which consists of two short 3D-printed parts designed to be clicked on the Geneva ovoid tubes. The parts are intentionally short to ensure the printability of the needle channels and have an opening at the top for inserting the Geneva ovoid tubes. The distal end of the top is extruded and features a click mechanism to secure the Geneva ovoid tubes. The ovoid tubes facilitate the IC structure of the applicator, whereas the 3D-printed parts contain curved needle channels to guide IS needles.

Working principle Concept 2
The 3D-printed parts are attached to the Geneva ovoid tubes in a manner similar to how ovoids are connected to the Geneva ovoid tubes. Guiding tubes are placed in slots in the distal end of the applicator parts. 6F ProGuide needles are inserted through the guiding tubes into the personalised curved needle channels. After inserting the needle in the patients' tissue, the nut of the guiding tube is tightened to lock the needle in position. To prevent needle channel mix-up, either a 3D-printed personalised bracelet or the currently used bracelet can be attached to the ovoid tubes. The current snap-fit mechanism of the Geneva ovoid tubes is used to assemble the parts to the the Geneva tandem.

Key aspects Concept 2

- **3D-printed parts**: the 3D-printed parts are designed short to ensure printability of the needle channels. The parts feature a click system for assembly to the Geneva ovoid tubes. No additional assembly steps need to be performed in comparison with the Geneva applicator;
- **Needle locking mechanism**: the needles are locked in position using the nut of the guiding tubes;

- **Visibility MRI**: three MRI markers can be used: one can be placed in the Geneva tandem and two in the Geneva ovoid tubes;
- **Intracavitary structure**: the IC structure is facilitated by the Geneva ovoid tubes, making the IC ovoid structure the only option;
- **Preventing needle channel mix-up**: a customised bracelet including numbers can be 3D-printed and clicked on the ovoid tube to separate the guiding tubes;
- **Assembly to Geneva tandem**: due to the fact that the Geneva ovoid tubes are used, the current snap-fit mechanism of the Geneva ovoid tubes can be used to assemble the parts to the the Geneva tandem.

Upon the creation of two conceptual designs, the simulation phase of the basic design cycle began.

5

Prototyping and final design

Prototypes were created for each concept design to further develop the designs. These prototypes contributed to the generation of the final designs for both concepts.

The new applicator will be manufactured by Oceanz using SLS printers EOS Formiga P1 system (EOS, Krailling, Germany) using polyamide 12 (PA12, EOS PA 2200, Krailling, Germany). PA12 is biocompatible for applications with surface contact and limited duration (<24 h) conform EN ISO 10993-1:2018 and has a high strength and stiffness [46]. After the printed applicator parts are cooled, the excessive powder is removed and the parts are cleaned with compressed air and a blasting agent. The parts will receive the vapour polish treatment. In this post-treatment, the 3D-printed parts are suspended in a vacuum process chamber. A solvent is introduced that slightly dissolves a thin layer of the surface of the parts. This creates a shiny and sealed surface. After smoothing, the solvent evaporates and the original material properties remain intact. In addition, vapour polishing ensures that the component remains impervious to dirt and can be easily cleaned [47].

5.1. Prototypes Concept 1

Figure 5.1 shows the main prototypes developed during the refining process of Concept 1. The prototype design iterations for Concept 1 are summarised in the flowchart presented in Figure 5.2. For a more comprehensive explanation of the prototyping process of Concept 1, see Appendix G.1.

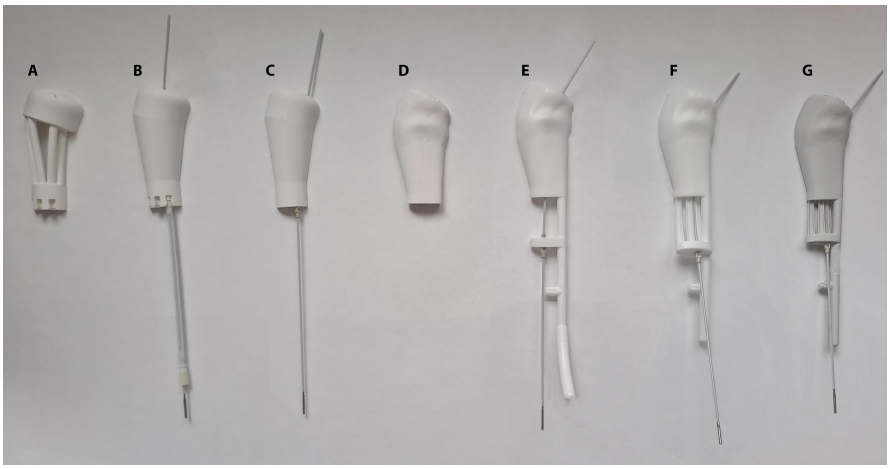


Figure 5.1: Prototypes of Concept 1 design iterations; (a) standard wireframe model with ovoid guiding tubes connection in entry region; (b) standard shell model; (c) standard shell model with needle lock pins in entry region; (d) personalised shell model; (e) personalised shell model with needle lock pins in bracelet; (f) personalised shell model with needle guiding tubes; (g) adjusted personalised shell model.

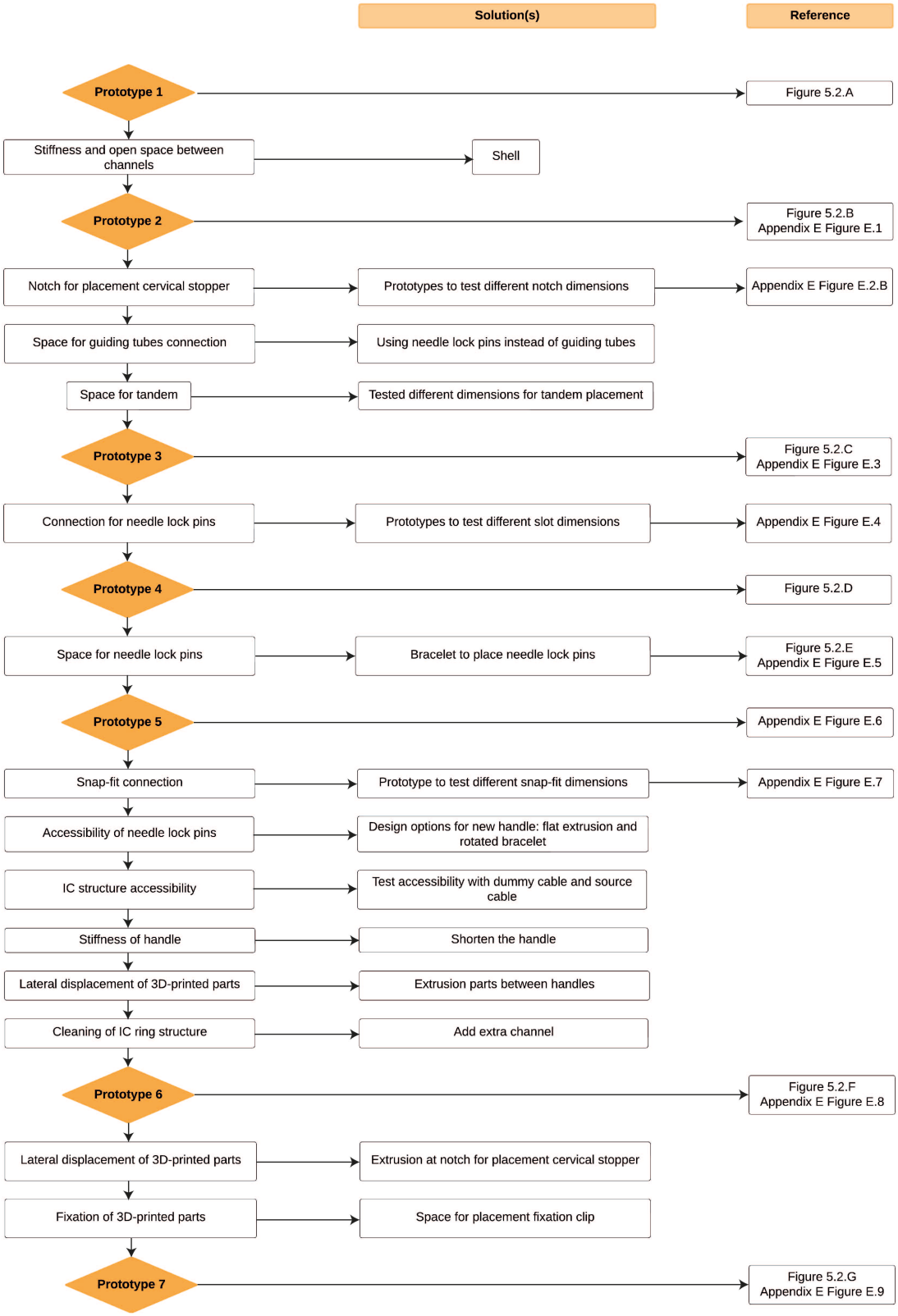


Figure 5.2: Flowchart of prototype design iterations of Concept 1: diamonds represent prototypes made, rectangles below diamonds signify associated problems. Second column contains the solutions to these problems and the third column indicates the corresponding figure in which the respective prototype is shown.

5.2. Prototypes Concept 2

Figure 5.3 shows the main prototypes developed during the refining process of Concept 2. The prototype design iterations for Concept 2 are summarised in the flowchart presented in Figure 5.4. For a more comprehensive explanation of the prototyping process of Concept 2, see Appendix G.2.

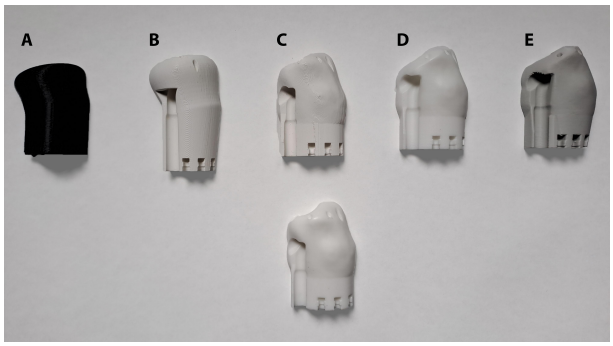


Figure 5.3: Prototypes of Concept 2 design iterations; (a) standard model with ovoid guiding tubes connection in entry region; (b) standard elongated model; (c) personalised model with adjusted guiding tubes insertion space (printed by Ultimaker and SLS); (d) personalised model with rounded top; (e) personalised model with tapered extrusion.

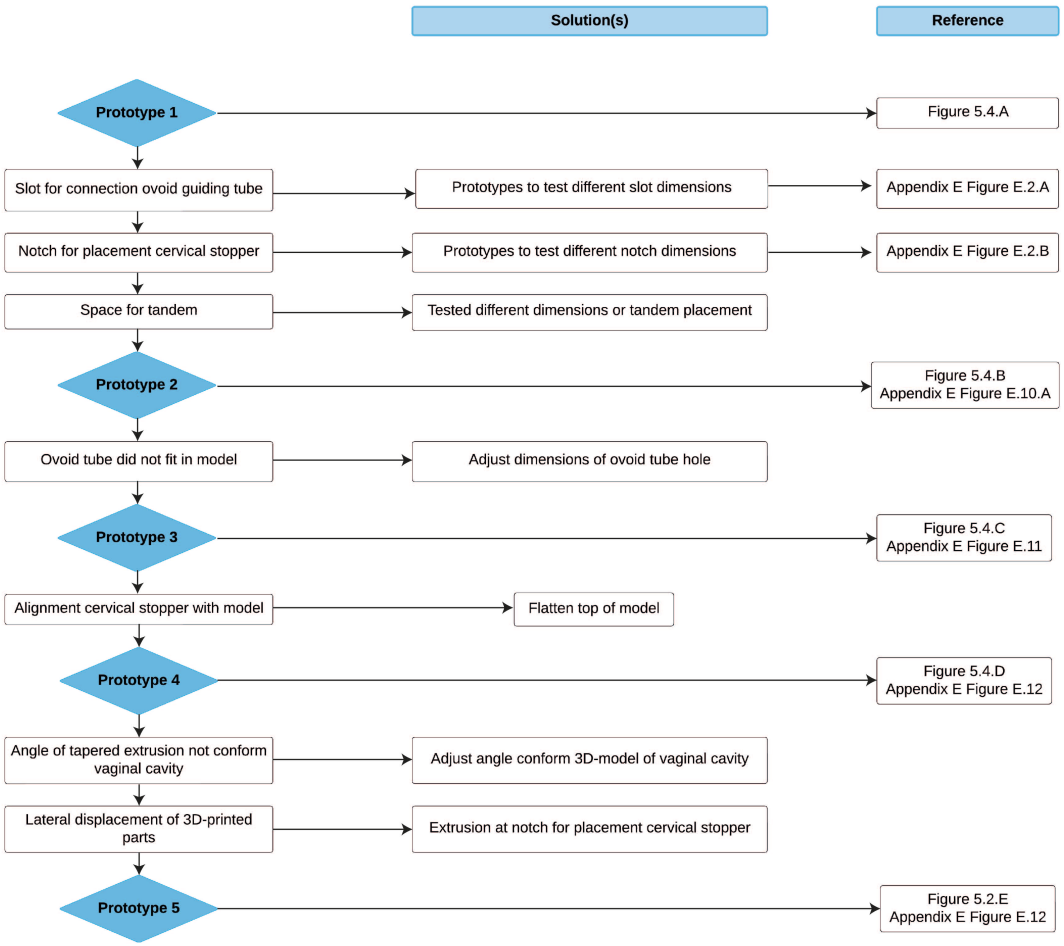


Figure 5.4: Flowchart of prototype design iterations of Concept 2: diamonds represent prototypes made, rectangles below diamonds signify associated problems. Second column contains the solutions to these problems and the third column indicates the corresponding figure in which the respective prototype is shown.

5.3. Final design Concept 1

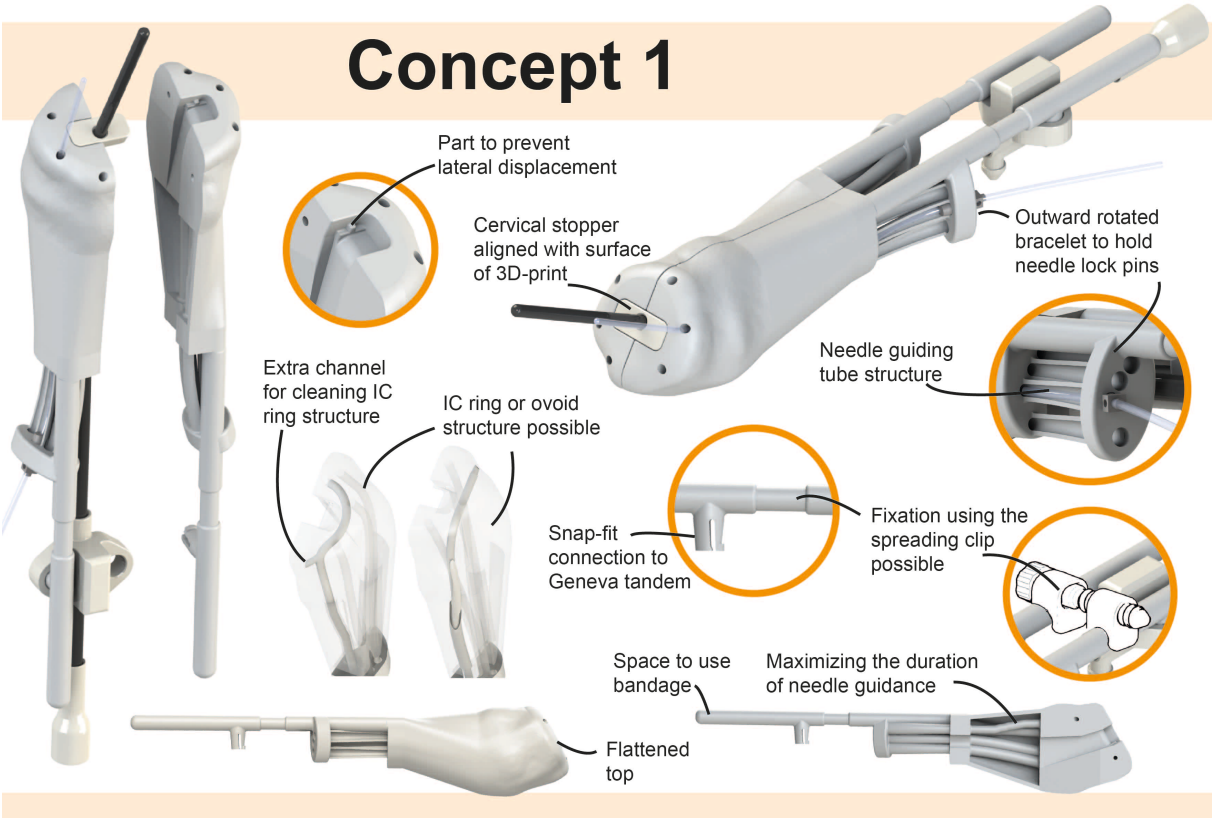


Figure 5.5: Final design Concept 1: two fully 3D-printed parts containing a personalised needle wireframe structure enclosed by a tailored shell. The top of the parts are flattened and contain an part to prevent lateral displacement. The length of the parts makes it possible to treat upper vaginal involvement and facilitates maximum needle guidance and there can be chosen between an IC ring or ovoid structure. Guiding structures guide the needles from the bracelet to the correct needle channel and the needle is locked using a needle lock pin.

The final design of Concept 1 and its features is shown in Figure 5.5. The design consists of two 3D-printed parts, each featuring a handle, snap-fit element, bracelet, guiding structures, entry region, wireframe structure, tailored shell, and a flattened top with a part to prevent lateral displacement of the 3D-printed parts.

Working principle Concept 1

6F ProGuide needles (obturator+catheter) are inserted though the bracelet and are guided by the guiding structures to the correct needle channels. Only a needle catheter is inserted in the IC structure. Needle lock pins are placed in the bracelet to lock the needles in position. The 3D-printed parts can be assembled to the Geneva fixation element using the integrated snap-fit mechanism. After assembly, lateral displacement of the 3D-printed parts is prevented by a small extruded part in the notch of the top. The 3D-printed parts can be fixated by placing the spreading clip on the handle. There is space available at the distal end of the handle for using a bandage to secure the applicator to the patient's legs.

Key aspects Concept 1

- **3D-printed parts**: guiding structures, composed of half tubes, guide the needles from the bracelet to the corresponding needle channels in the entry region of the 3D-print. The bracelet is connected to the handle and is rotated outward to ensure that the needle lock pins can be inserted into the bracelet and can be locked using the needle lock tool. An extra channel is added in the top, extending from the IC ring structure, to enhance the accessibility for cleaning the channel. The top of the 3D-printed parts is flattened conform a ring applicator to ensure proper placement of the parts against the fornices. The notch in the top of the 3D-printed part features a small extrusion part which prevents the 3D-printed parts from displacing laterally after assembly;

- **Needle locking mechanism**: needle lock pins inserted in holes in the bracelet are used to lock the needles in position;
- **Visibility MRI**: one MRI marker can be placed in the Geneva tandem. A radiotherapy technologist stated that this is likely sufficient to reconstruct the applicator on the MRI;
- **Intracavitary structure**: see key aspect 'intracavitary structure' in Section 4.2.1;
- **Preventing needle channel mix-up**: the guiding structures guide the needle from the bracelet to the corresponding channel in the entry region. As a result, attention only needs to be paid to which bracelet hole the needle is inserted into;
- **Assembly to Geneva tandem**: see key aspect 'assembly to Geneva tandem' in Section 4.2.1.

5.4. Final design Concept 2

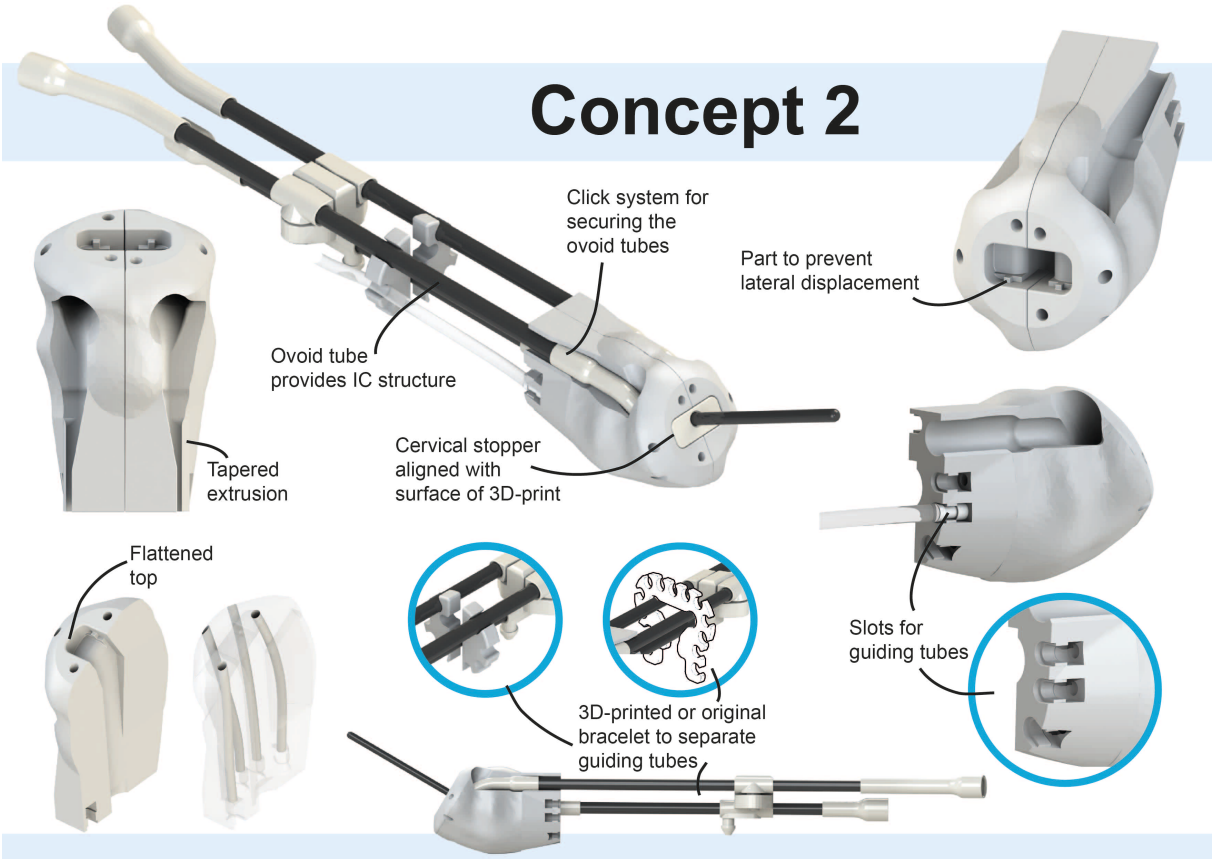


Figure 5.6: Final design Concept 2: two short 3D-printed parts with a tapered extrusion conform the shape of the patients' vaginal cavity. The part can be clicked on the Geneva ovoid tubes, which provide the IC structure. The short length of the parts ensure printability of the needle channels. IS needles can be inserted through guiding tubes which are clicked in the distal end of the 3D-printed parts. To prevent needle channel mix-up, a customised bracelet can be 3D-printed and clicked on the ovoid tube to separate the guiding tubes.

Figure 5.6 presents the final design of Concept 2 along with its features. The design consists of two 3D-printed parts, featuring a tapered extrusion from the distal ends to match the vaginal cavity's geometry. The top of the parts are flattened and include a part to prevent lateral displacement of the applicator parts.

Working principle Concept 2
The working principle of the final design of Concept 2 does not differ from the initial Concept 2 design, and can be found in Section 4.2.2.

Key points Concept 2

- **3D-printed parts**: the angle of the tapered extrusion at the distal end of the 3D-printed parts is conform the shape of the patient's vaginal cavity. The top of the 3D-printed parts is flattened conform a ring applicator to ensure proper placement of the parts against the fornices. The notch in the top of the 3D-printed part features a small extrusion part which prevents the 3D-printed parts from displacing laterally after assembly;
- **Needle locking mechanism**: see key aspect 'needle locking mechanism' in Section 4.2.2;
- **Visibility MRI**: see key aspect 'visibility MRI' in Section 4.2.2;
- **Intracavitary structure**: see key aspect 'intracavitary structure' in Section 4.2.2;
- **Preventing needle channel mix-up**: see key aspect 'preventing needle channel mix-up' in Section 4.2.2;
- **Assembly to Geneva tandem**: see key aspect 'assembly to Geneva tandem' in Section 4.2.2.

6

Evaluation

To investigate the potential value of the two final designs, four evaluations have been conducted. The dose attenuation properties of PA12 were examined, the possible needle placement options in the top of the two concepts have been investigated, the feasibility of the workflow for the personalised applicator generation have been validated and the usability of the two concept designs was assessed by three radiotherapist-oncologists.

6.1. Material evaluation: dose attenuation properties of PA12

To be able to use PA12 as the material for the applicator, it must be validated if PA12 has the same radiation dose attenuation properties as water. Radiation dose attenuation properties refer to how well a material can absorb or attenuate radiation. When radiation interacts with water, it undergoes similar processes such as scattering and absorption as it would within biological tissues. Therefore, when the applicator material has similar dose attenuation properties to water, it ensures that the radiation dose distribution calculated during treatment planning accurately represents the dose distribution that would occur within actual biological tissue. Clinical BT dose distributions are calculated based on the American Association of Physicists in Medicine (AAPM) Task Group #43 (TG-43) protocol [48]. TG-43 defines a 2D dose calculation formalism which specifies the dose rate in water from a BT source.

To evaluate the radiation attenuation properties of PA12, the experimental setup described in the article of Cunha et al. in which the radiation attenuation properties of PC-ISO were evaluated, is used [49]. This experimental set up was chosen because the medical physicist and the radiotherapy technologist that helped with the experiment already had experience with the set-up. Furthermore the setup is simple and therefore the experiment is easily reproducible. The radiation attenuation properties of PA12 will be evaluated by comparing the percent dose depth curve obtained from the radiochromic film test for the designed PA12 testing apparatus and a control apparatus. For the complete protocol of the experiment, see Appendix H.1.

Method

The two test boxes used in the article of Cunha et al. were recreated using SolidWorks 2022 [49]. The test boxes consist each of two L-shaped parts. The first box had a closed surface and was used to measure the dose attenuation properties of Oceanz PA12 (Figure 6.1A). The second box had an open surface and was used to make the comparison with the dose attenuation properties of water (Figure 6.1B). Both boxes were printed in PA12 by Oceanz using SLS. After printing and cooling, box 1 received a vapour treatment to make the material more waterproof.

Figure 6.1: The two test boxes used during the experiment; (a) test box 1 with closed surface; (b) test box 2 with open surface; (c) schematic illustration of test box 1 with placed Gafchromic film segment and flexible implant tube inserted in the needle channel: 1. Flexible implant tube; 2. Test box 1; 3. Gafchromic film segment.

A total of seven Gafchromic type EBT3 film segments, measuring 4.5cm x 6cm with a thickness of 0.28mm, were cut and were in turn placed inside one of the testboxes. There was one test film segment and six segments were used for analysis. The flexible implant tube was inserted inside the source channel of one of the testboxes. The button at the end of the flexible implant tube was taped to the test box to prevent it from moving during the irradiation. To prevent the effect of radiation scattering by the floor on the film segment, the test box was taped to a plastic PET bottle filled with water which was placed in the middle of a water tank. The flexible implant tube was connected to the transfer tube and the afterloader, see Figure 6.2. This connection must always be outside the water tank to avoid damage to the source and/or afterloader. For a detailed explanation of the method of the experiment, see Appendix H.1.

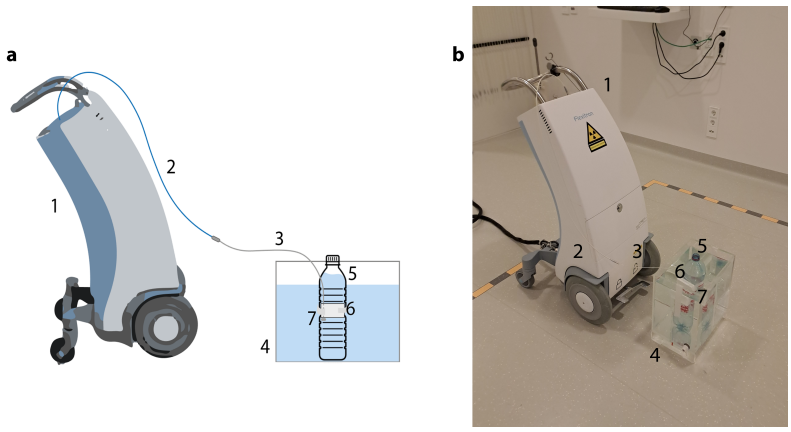


Figure 6.2: Experimental set-up; (a) schematic illustration of experimental set up: (b) photo of experimental set up; 1. Flexitron afterloader; 2. transfer tube; 3. flexible implant tube; 4. water tank; 5. PET bottle; 6. test box 1; 7. tape.

All film segments were irradiated with the same irradiation plan, which was set to deliver 1500 cGy at 1 cm radially from the center of the source channel. After it was validated with the test film segment that the setup functioned, the other six films segments were irradiated. Three of the six film segments were placed inside test box 1 (PA12), the other three segments were placed inside test box 2 (water). The film segments were allowed to self-develop for 24 hours after irradiation.

After development, all six film segments were scanned using a flatbed colour scanner (3x16 bit, 300 dpi). The scans can be seen in Figure 6.3.

Results

As can be seen in Figure 6.3, not every film segment is the exact same size and straight due to cutting and scanning of the segments. Therefore, before analysing the segments, the uncut 4cm side of each segment is placed vertically in Photoshop. Next, the scans were cropped to 1.5cm x 6cm from the middle of the uncut 4 cm resulting in a strip of the centre of the film segment. It was validated that the dose profile of the resulting strip was relatively flat. The resolution of the segments was lowered to 72 dpi to reduce noise and the films were saved as .tif files.
A code in which the six .tif files were loaded was written in Matlab (R2021b, Mathworks, Natick, Mas-

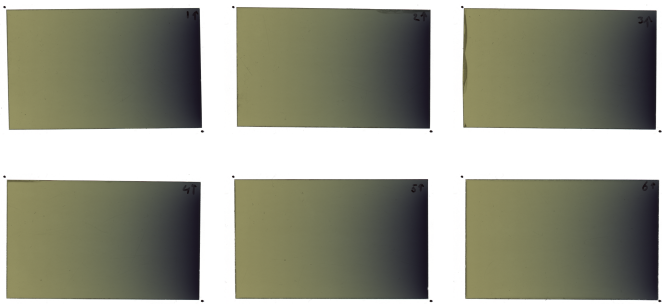


Figure 6.3: Scans of the six irradiated film segments. Upper row: film segments 1, 2 and 3 (irradiated in test box 1: closed surface); lower row: film segments 4, 5 and 6 (irradiated in test box 2: open surface).

sachusetts, United States), see Appendix H.4. The grey values of each colour channel (R G and B) of each pixel of the film segments were obtained. With these grey values, the optical density of each channel of each pixel were calculated using:

$$\text{Optical Density (OD)} = \log_{10}\left(\frac{2^{16}}{\text{greyvalue}}\right)$$

The optical density quantifies the amount of radiation absorbed by the film segment. With the optical density of each colour channel of each pixel, the dose in mGy was calculated using:

$$\text{Dose} = -\left(\frac{a - c \cdot 10^{-OD}}{b - 10^{-OD}}\right)$$

In which the parameters depend on the colour channel as listed in table 6.1.

Table 6.1: Fitparameters per colour channel used for calculating the dose.

	R	G	B
a	1532.3523	3447.46	5470.2997
b	0.062625	0.0029012	0.063173
c	4021.4852	5809.5425	14271.19

The values of these parameters were already defined using a calibration file. Next, the average dose of the three colour channels is calculated and the dose is converted from mGy to Gy. The average dose per pixel of the film segments is shown in Figure 6.4.

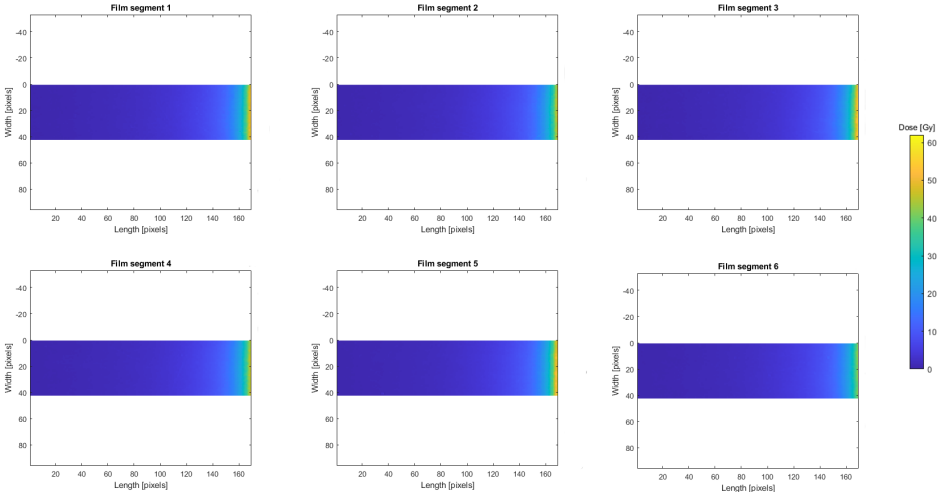


Figure 6.4: Dose per film segment. Upper row: dose in film segments 1, 2 and 3 (irradiated in test box 1: closed surface); lower row: dose in film segments 4, 5 and 6 (irradiated in test box 2: open surface).

To be able to obtain the percent dose-depth curve, the average of the dose per pixel column and the average of the first three film segments (PA12) and of the last three segments (water) were calculated see Figure 6.5A. The dose percentage was calculated using the maximum dose value per film segment. The pixel length was converted into cm and the average of the percent dose depth curves of PA12 and water were calculated and plotted, see Figure 6.5B.

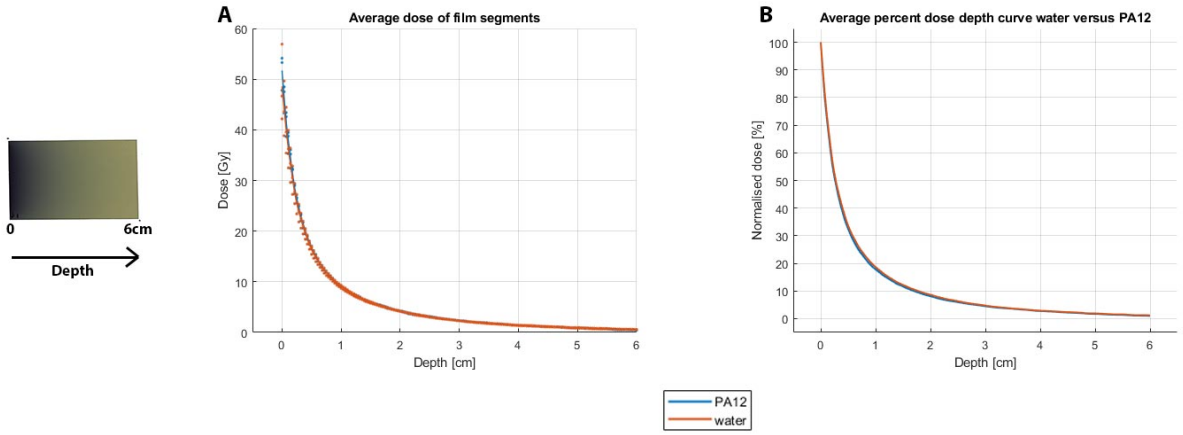


Figure 6.5: Results of dosimetry experiment. (a) average dose of all six films segment (points in the graph) and the average of PA12 and water (blue and orange lines, respectively); (b) average of percent dose depth curves of PA12 and water (blue and orange lines, respectively). Note: the depth of the film segment was measured from the side that was positioned adjacent to the source channel.

For the comparison between the two percent dose depth curves, points closer than 1cm were excluded because that region of the film was oversaturated [49, 50]. The maximum and mean difference between the average percent dose depth curves of water and PA12 are 0.8% and 0.3%, respectively. This indicates that the difference at identical depths does not exceed 0.8 between the average percent dose depth curve of water and PA12. This observation indicates that the two percent dose depth curves maintain a difference of less than 1% between 1cm and 6cm from the source. In accordance with Cunha's statement, this can be considered a water-equivalent response [49].

6.2. Applicator top geometry and possible needle planning options

The potential number of needles that can be placed in the personalised applicator and the possible needle channel positions depend, among other things, on the implemented IC structure in the personalised applicator and on its top geometry.

The top geometry of the personalised applicator is affected by the size of the Geneva or Venezia applicator that is used during the first fraction. The Geneva and Venezia applicator are available in different sizes which correspond to the distance between the centre line of the IC structure, as depicted with L1 in Figure 6.6A-B. L2 in Figure 6.6A represents the distance between the centre line of the IC ovoid channels and the outer surface of the ovoids, which has a fixed distance of 10mm. In the Venezia applicator, the fixed distance between the IC ring channel and the outer surface of the ring is 6mm (L2 in Figure 6.6B). The height of the Venezia applicator depends on the used ring size, whereas the height of the ovoids in the Geneva applicator have a height of 30mm, independent of the ovoid size that is used. These differences lead to variations in the total width and height of the top of the Geneva an Venezia applicators, as is listed in Table 6.2.

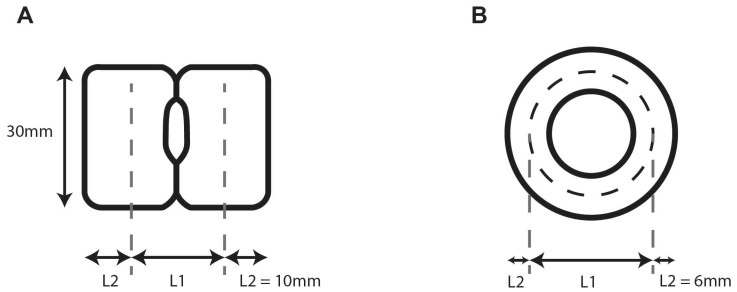


Figure 6.6: Dimensions of (a) Geneva ovoids and (b) Venezia ring. L1 indicates the distance between the center lines of the IC structures, L2 the distance between the center line of the IC structure and the outer surface of the applicator.

Table 6.2: Differences in available sizes of the Geneva ovoids and Venezia ring and their total width in mm.

Geneva		Venezia	
Applicator size L1 [mm]	**Total width [mm]**	**Applicator size L1 [mm]**	**Total width [mm]**
15	35	22	34
20	40	26	38
25	45	30	42
30	50		
35	55		
40	60		

In Concept 1, there can be chosen to implement an IC ring or ovoid structure in the personalised applicator. The position of the IC structure affects the dose distribution. Due to this and the differences stated above, consideration is needed when deciding which IC structure to implement in the personalised applicator.

Figure 6.7 illustrates the possible needle positions at the top surface of the personalised applicator, for both Concept 1 and Concept 2, when using a 22mm Venezia and 15mm Geneva applicator during the first fraction. As can be seen in the figure, using a Geneva applicator results in a more wider top geometry. A wider applicator top can be an advantage in patient cases where oblique needles are desired (e.g. patient with bulky tumours or parametrial tumour invasion). As can be seen in 6.7A, with the 22mm Venezia IC ring structure implemented in the applicator, it will not be possible to place a needle inside the IC ring structure. This can be a disadvantage in patient cases with small or centrally located tumours. Nevertheless, when one of the larger Venezia ring sizes is used, it will be possible to place a needle inside the ring structure. Figure 6.7C indicates that in Concept 2, due to the use of the ovoid tubes and the space they require for insertion, a specific area of the top surface is no longer accessible for needles.

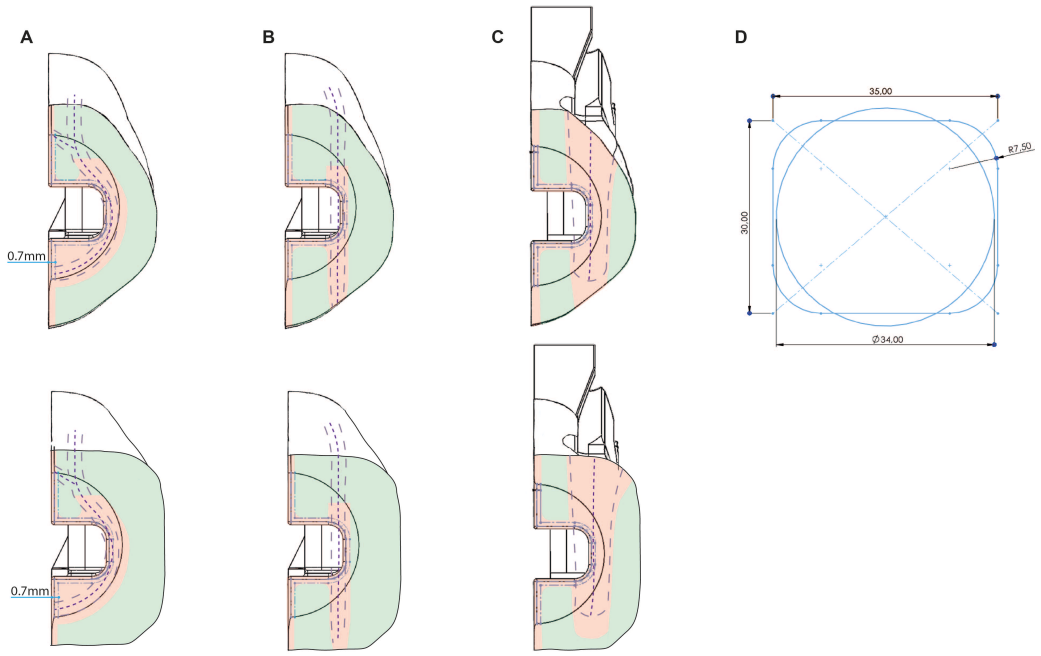


Figure 6.7: Possible needle positions at the top surface of the two concepts. (a) Concept 1 with integrated 22mm IC ring structure; (b) Concept 1 with integrated IC ovoid structure; (c) Concept 2 with IC ovoid tubes; (d) difference in top geometry when using a 15mm Geneva or a 22mm Venezia applicator. Upper row shows the top geometry in case a 22mm Venezia applicator is used for the first fraction. Lower row shows the top geometry in case a 15mm Geneva applicator is used for the first fraction. Green sections indicate where needle placement is possible, red sections indicate where needle placement is not possible. The dotted lines represents the IC structure.

Figure 6.8 shows examples of IS needle channel placement in the top of both concepts. There are certain constraints which affect the needle placement options in the 3D-printed parts. For example, Oceanz recommends a wall thickness of 0.7mm for PA12, which means that the channels should be located 0.7mm from the applicator's surface [51]. Furthermore, the insertion force analysis done by Laan et al. yielded a needle channels radius constraint of 35mm to minimise the risk on needle jamming or buckling [24]. Due to this radius constraint, implementing certain needle channel curvatures could be more challenging in shorter 3D prints, such as in Concept 2.

Figure 6.8: Examples of needle channel placement in the two concepts; (a) Concept 1 with 22mm IC ring structure and 3 IS needles; (b) Concept 1 with IC ovoid structure and 3 IS needles; (c) Concept 2 with ovoid tubes as IC structure and 4 IS needles.

6.3. Workflow validation

As explained in Section 3.5 and illustrated in Figure 3.3, the development of the personalised applicator involves new process steps. To assess the feasibility of the new applicator's workflow, a workflow validation process was conducted. This process included step 1 (imaging) till step 11 (pre-use checks) of the process tree (see Figure 3.3). For the MRI images of the first fraction (step 1: imaging), the commercially available OB/GYN Pelvic Phantom was used (Viomerse OB/GYN Pelvic Phantom, Pittsford, NY, USA). This phantom consists of a plastic frame holding a hydrogel structure which features a vagina, vaginal vault, uterus with cervix, urethra, bladder and rectum. In addition, the phantom is CT and MRI compatible. Figure 6.9 presents the workflow validation steps that were conducted.

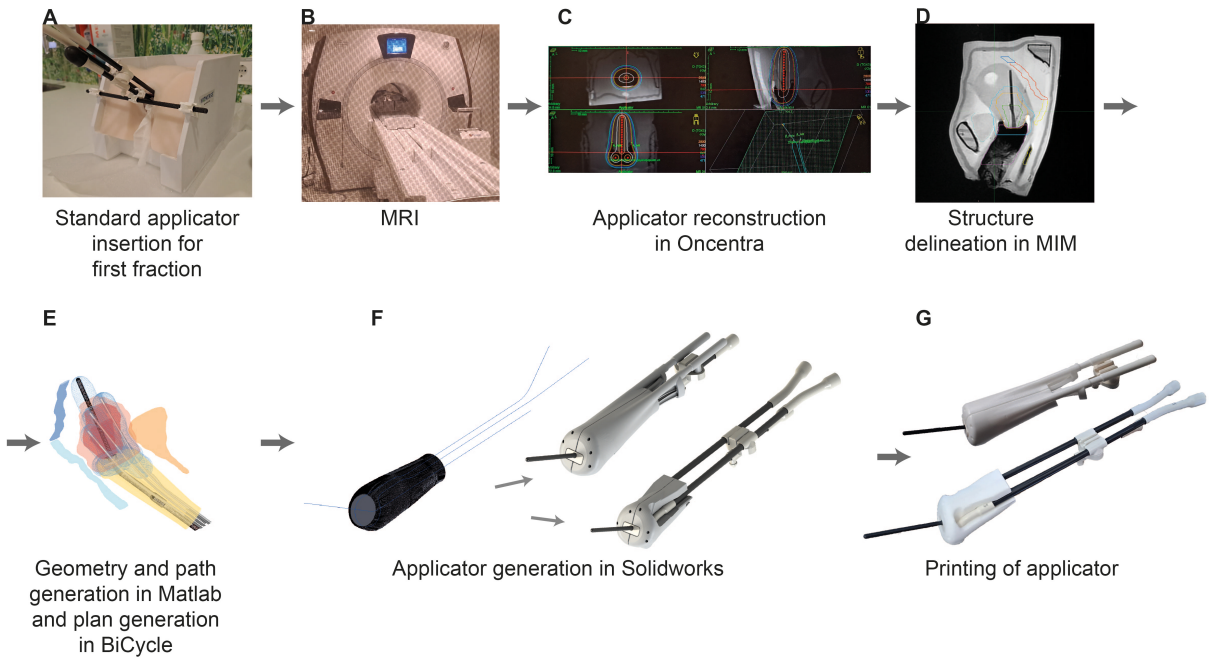


Figure 6.9: Completed steps during the workflow validation; (a) insertion of Geneva applicator in phantom; (b) imaging of phantom; (c) reconstruction of applicator; (d) structure delineation; (e) trajectory planning; (f) personalised applicator modeling; (g) printing of applicators.

First fraction MRI
Based on MRI images of the phantom provided by Viomerse, the 80mm Geneva tandem and the 25mm ovoid pair were chosen to use for insertion. The Geneva tandem was inserted in the vaginal cavity of the phantom, reaching into the phantom's uterus. The positioning of the tandem in the uterus was validated using a CT scanner (Siemens SOMATOM confidence; Siemens Healthcare AG, Erlangen, Germany) as shown in Figure 6.10. Following validation of correct placement of the tandem, the ovoid tubes and the 25mm ovoid pair were inserted and assembled to the Geneva tandem. To prevent displacement of the applicator, the tandem was fixated to the plastic sides of the phantom using 3D-printed clamps and plastic screws.

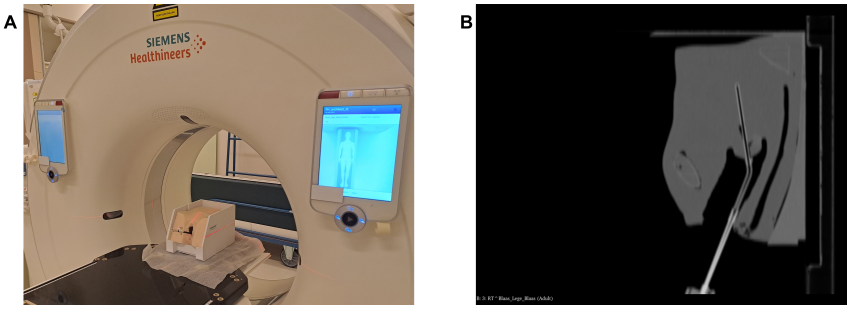


Figure 6.10: Placement validation of tandem; (a) phantom with Geneva tandem in the CT scanner; (b) corresponding CT scan showing correct positioning of the tandem in the uterus.

A radiotherapist-oncologist from Erasmus MC stabilised the applicator inside the vaginal cavity using vaginal packing (Figure 6.9A). The phantom with Geneva applicator and packing inserted was placed in the MRI scanner (Figure 6.9B). Similar sequences as used in patient treatment were included in the MRI protocol: sagittal and axial T2-weighted sequences, and transverse Fiesta sequence.

Reconstruction of applicator
A radiotherapy technologist imported the Fiesta scan into the clinical treatment planning system Oncentra-Brachy (version 4.6.0, Elekta AB, Stockholm, Sweden) and reconstructed the applicator. Following reconstruction of the applicator, a standard treatment plan was generated (Figure 6.9C).

Delineation of structures in MIM
The axial and sagittal T2 MRI scans were loaded in MIM Research (Version 7.1.6; MIM Software, Inc, Cleveland, OH). Based on these images, the following structures were delineated: bladder, rectum and vaginal cavity, as depicted in Figure 6.9D and 6.11. To be able to generate a personalised treatment plan and to generate the personalised applicator needle channels, also the bowel, sigmoid, GTV, HR-CTV and IR-CTV delineations are needed. As these structures were not present in the phantom, they were delineated based on anatomical knowledge and using an anonymous patient case as reference.

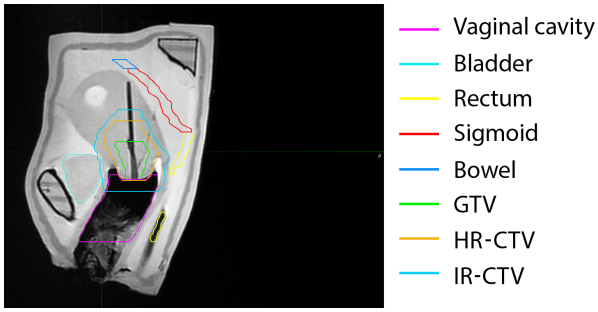


Figure 6.11: Screenshot of MIM showing the delineated OARs and target volumes.

Applicator geometry generation, path planning and plan generation in Matlab
A PhD researcher created a Matlab algorithm (R2021b, Mathworks, Natick, Massachusetts, United States) which interpolates the structure contours to obtain meshes. The structures were smoothed and simplified. The shape of the personalised applicator was based on the mesh of the vaginal cavity. A Venezia 26mm IC ring structure was integrated in the personalised applicator geometry. Based on the structures of the GTV, HR-CTV, IR-CTV and the OAR, the algorithm generated and optimised IS needle channels inside the applicator geometry which were saved as txt file. Figure 6.9E illustrates the outcome in Matlab.

Applicator model generation in SolidWorks
The mesh of the personalised applicator geometry made by the Matlab algorithm was exported to a STL file and imported in SolidWorks 2022. The centre line of the tandem and the IC ring channels were inserted as curve by importing their txt files. The left model of Figure 6.9F shows the resulting Solidworks model. The two right models of Figure 6.9F show the generated applicator models of Concept 1 and Concept 2.

Printing of applicators
The two applicator models were exported to STL files and sent to Oceanz to be manufactured. After printing and cooling of the models, they were cleaned with compressed air and a blasting agent, and received the vapour polish treatment.

The workflow validation process suggests that the workflow of the personalised applicator is feasible. Nevertheless, the following aspects led to some difficulties during the process: the the mesh smoothing done in Matlab, the SLS printing accuracy and post-processing of the printed prototypes.

6.4. Harris Profile

To graphic represent the strength and weaknesses of the two concepts, a Harris profile was completed, see Table 6.3. The six criteria that are used for evaluation are based on the key aspects defined during the concept generation in Section 4. A four-point scale is used to score the criteria, ranging from -2 (bad) to +2 (good). The scores represent an assessment of how the concept meets the criteria and is based on the outcomes of the needle planning option evaluation and workflow validation process. The reasoning of the provided scores can be found in Appendix I. Based on the given scores, Table 6.3 suggests that Concept 1 is the most promising design.

Table 6.3: Harris profiles of the two concept designs.

Criteria	Concept 1				Concept 2			
	-2	-1	+1	+2	-2	-1	+1	+2
1. Possible IS needle planning options				■		■		
2. Needle insertion			■					■
3. Needle locking system			■					■
4. Printability/cleanability of the needle channels			■					■
5. Reconstruction of applicator on MRI			■					■
6. Component to reduce channel mix-up				■		■		

6.5. User experience experiment

In order to validate the working principles of the two concepts and to identify design improvement points, a user validation experiment was established. Three radiotherapist-oncologists from Erasmus MC inserted the two concept prototypes in the Viomerse phantom and gave their feedback about the designs. The Human Research Committee (HREC) of the TU Delft provided their approval for the experiment. The initial experiment protocol can be found in Appendix J.

Purpose
The purpose of the experiment was to identify design improvement points by evaluating how an experienced applicator user (radiotherapist-oncologists) handles the two 3D-printed prototypes during insertion in the phantom and assembly to the Geneva tandem.

User task
The radiotherapist-oncologist were asked to insert a needle in one of the channels till the surface of the prototypes and to lock the needle. The radiotherapist-oncologists positioned the applicator in the phantom and assembled it to the Geneva tandem, which was already inserted in the phantom prior to the experiments. Figure 6.12 shows the prototype of concept 1 inserted in the phantom by one of the radiotherapist-oncologists during the experiment. After placement, the radiotherapist-oncologists were allowed to use vaginal packing to stabilise the applicator. For each prototype, the radiotherapist-oncologists were asked to fill in a questionnaire.

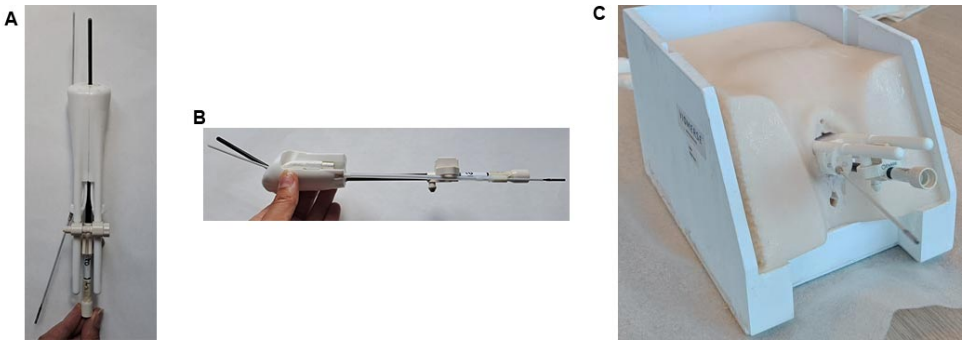


Figure 6.12: 3D-printed prototypes and the phantom used during the user experience experiment; (a) prototype of Concept 1 with needle inserted; (b) prototype of Concept 2 with needle inserted; (c) prototype of Concept 1 placed in phantom by radiotherapist-oncologist during experiment.

Evaluation criteria
The questionnaire consisted of five questions that required responses on a 5-point scale, along with seven open-ended questions and the System Usability Scale (SUS). The SUS provides a 'quick and dirty', reliable tool for measuring the usability of products and contains ten questions that need to be answered on a 5-point scale [52]. The questions were about various design aspects of the prototypes and their working principles. Feedback was asked on the following aspects: the overall design of the applicator, the used needle locking mechanism, the method of assembling the 3D-printed parts to the Geneva tandem (proximal and distal connection), the ease of holding and manoeuvring the applicator within the vaginal cavity, stabilisation of the applicator, what they like and dislike about the design and their main concern about the design. The questionnaire also provided space for additional feedback.

User feedback
Radiotherapist-oncologist 1 provided verbal feedback during the experiment, whereas radiotherapist-oncologists 2 and 3 also completed the questionnaire. The complete feedback provided by the radiotherapist-oncologists and their completed questionnaires can be read in Appendix K. Based on the provided feedback, two tables have been created: Table 6.4 lists the evaluation criteria on which all three radiotherapist-oncologists provided similar feedback while Table 6.5 highlights criteria where their feedback differed.

Table 6.4: Evaluation criteria on which the three radiotherapist-oncologists provided similar feedback.

Criterion	Prototype Concept 1	Prototype Concept 2
Needle insertion	Needle insertion through the lock pin requires much force	Placing a needle through the guiding tubes is straightforward

Continued on next page

Table 6.4: Evaluation criteria on which the three radiotherapist-oncologists provided similar feedback. (Continued)

Needle locking mechanism	When the needle lock pin is placed in the bracelet and a needle is inserted, it is impossible to turn the pin to lock the needle	Locking the needles using the nut of the guiding tubes is not difficult
Holding and manoeuvring the applicator	Easy to hold and place in phantom	Because the 3D-printed parts do not connect properly to the ovoid tubes (not firm enough), placement is more challenging because the parts may disconnect from the ovoid tubes
Fixation of the prototypes	It is expected that the spreading clip will not be necessary as the applicator is personalised and hence provides a snug fit. Use of the fixation clip is desired, this is currently not possible	Fixation clip is used to fixate the ovoid tubes to the ovoid tubes to the Geneva tandem

Table 6.5: Evaluation criteria on which the three radiotherapist-oncologists provided differing feedback.

	Prototype Concept 1	**Prototype Concept 2**
Criterion: Design		
Radiotherapist-oncologist 1	The entry region that extends beyond the introitus is likely to be uncomfortable for the patient	The click-system to connect the parts to the ovoid tubes is not secure enough
Radiotherapist-oncologist 2	Because the entry region extend beyond the introitus, the sharp edges of the entry region and guiding structures are outside the patient, as desired. Additionally, it is possible to see in which channel the needles are located. The long distal extrusion of the handle beyond the fixation element, indicated for use of bandage, is not necessary	There are sharp edges at the caudal and ventral position of the 3D-printed parts, which can cause discomfort and injury to the patient
Radiotherapist-oncologist 3	Easy to use	Easy to use
Criterion: Stabilisation of the assembled applicator		
Radiotherapist-oncologist 1	No vaginal packing seems needed	No vaginal packing seems needed
Radiotherapist-oncologist 2	No vaginal packing seems needed	Vaginal packing seems needed
Radiotherapist-oncologist 3	No vaginal packing seems needed	Vaginal packing seems needed
Criterion: Main concerns about the design		
Radiotherapist-oncologist 1	Force needed to insert needles through the needle lock pins and through the 3D printed parts and locking the needles	Firmness of click-mechanism used to connect the 3D-printed part to the ovoid tubes
Radiotherapist-oncologist 2	The length of the 3D-printed parts if vaginal reference length is long and the number of needles that can be used	Insertion and the sharp edges at ventral position of the 3D-printed parts which can cause discomfort and injury to the patient
Radiotherapist-oncologist 3	Force needed to insert needles through the needle lock pins and the fact that the needle insertion tool is not applicable in this design	Firmness of click-mechanism used to connect the 3D-printed part to the ovoid tubes

The feedback provided by the three radiotherapist-oncologists suggests that in Concept 1 it is desirable to use the fixation clip to fixate the 3D-printed parts to the Geneva tandem. Vaginal packing and the spreading clip are unlikely to be used in this concept. Furthermore, the feedback indicates that the click-mechanism in Concept 2, which is used to attach the 3D-printed parts onto the ovoid tubes, is not secure enough. Therefore, these aspects need to be further investigated. Two of the three radiotherapist-oncologists completed the SUS questions. Therefore, it was decided to not analyse the SUS scores.

The user experience evaluation brought to light a design flaw in Concept 1: the needle lock pins got compressed once inserted into the bracelet. Consequently, a considerable amount of force was needed to insert a needle through the pins and to rotate the pins to lock the needle in position. As a result, the locking system did not function correctly during the experiments. Furthermore it was noted during the experiment that not all radiotherapist-oncologist were familiar with the use of the needle lock pins.

6.6. List of requirements fulfillment

Table 6.6 gives an overview of the list of requirements and whether the requirements have been fulfilled by the two designs. For both designs, 16 of the 22 requirements were fulfilled, 1 was not met and 5 requirements were not tested. For Concept 1, the two wishes are fulfilled, in contrast to Concept 2 for which both wishes were not fulfilled.

Table 6.6: Fulfilment of list of requirements.

Performance requirements (A)			
No.	**Requirement**	**Requirement fulfilment**	**Explanation**
A.1	The applicator shall have the ability to guide 6F needles (obturater+catheter) or flexible implant tubes.	Yes	In the two designs it is feasible to place 6F needles and flexible implant tubes through the designated channels. However, the user experience experiment revealed that the needles still encounter substantial friction during insertion.
A.2	The applicator shall have the ability to lock 6F needle catheters.	Yes	Following step 4.3 'Insert the Needles' from the Martinez Prostate Template Set Instructions for Use provided by Elekta, the needles are locked when the needles do not shift when pulled gently [53]. This has been validated in both designs. However, it was found challenging in design 1 to insert the needle lock pins into the bracelet and subsequently insert a needle through it. This was due to the dimensions of the needle lock holes.
A.3	The applicator shall have the ability to guide needles into the parametrium and upper vagina.	Concept 1: yes Concept 2: no	Concept 1 does have the ability to guide needles into the upper vagina and parametrium. However, due to the length of the 3D-printed parts in Concept 2, this concept does not have the ability to guide needles into the upper vagina. In addition, the shorter length also makes it more difficult to guide needles into the parametrium due to the curvature constraint of the needle paths.
A.4	The 3D-printed part(s) of the applicator shall not disassemble or break under a vertical and horizontal load of 15N applied to the distal end of the 3D-printed parts.	Not tested	Due to the high strength and stiffness (tensile strength: 48 MPa) of Oceanz PA12, no problem is foreseen regarding this requirement [46]. However, it should be tested (e.g.destructive testing).

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Table 6.6: Fulfilment of list of requirements. (Continued)

A.5	The 3D-printed part(s) of the applicator shall not deform or break when falling of a height of 2 meters.	Not tested	Due to the high strength and stiffness (tensile strength: 48 MPa) of Oceanz PA12, no problem is foreseen regarding this requirement [46]. However, it should be tested.
A.6	The applicator shall obtain a pear shaped isodose configuration.	Yes	Both concepts include an IC structure based on IC structure of the Geneva or Venezia applicator and both concepts include the Geneva tandem. Therefore, it is validated by design that the applicator shall obtain a pear shaped isodose configuration.
A.7	No uncured residues shall be left in the source channels after fabrication of the applicator.	Concept 1: no Concept 2: yes	Even though in concept 1 an extra channel connected to the IC ring structure is added, it was found that sometimes it is still not possible to get all uncured residues out of the channel.
A.8	The applicator shall be able to be assembled to a Geneva tandem.	Yes	
A.9	The needles within the applicator shall be able to be connected to the Flexitron afterloader.	Yes	
A.10	The applicator shall be able to be immobilised within the vaginal cavity.	Yes	
A.11	The applicator should include a component to prevent channel mix-up.	Yes	Both concepts contain an element which should contribute to reducing needle channel mix-up. However, there is not validated whether it actually reduces needle channel mix-up.
Environment requirements (B)			
B.1	Performance of the 3D-printed parts shall not noticeably be negatively affected inside temperature range of -20 °C to 60 °C and humidity of 90%.	Yes	The melting temperature of Oceanz PA12 is 185-189 °C [46].
Life in service requirements (C)			
Size and weight requirements (D)			
D.1	The applicator parts shall be insertable through a P5 introitus (L-R width: 19 mm).	Not tested	Potential placement issues within a P5 introitus might arise using Concept 2: due to the curvature in the ovoid tube, the proximal end the tube has a width of about 25mm. potential placement issues within a P5 introitus might arise.
D.2	The surface of the 3D-printed part(s) shall not cause any harm to the patient throughout the entire procedure.	Not tested	During the applicator design process in SolidWorks, fillets are added to the edges of the applicator. In addition, due to the SLS printing process, all edges and corners of the prototypes will get a radius of ±0.4mm [54].
Materials requirements (E)			
E.1	The material(s) of the applicator shall be MRI and CT compatible.	Yes	
E.2	The material(s) of the 3D-printed parts shall not cause distortions or artefacts on MRI and CT scans.	Not tested	Since the personalised applicator is made of a plastic it is not expected to cause distortions or artefacts on MRI and CT scans.

Continued on next page

Table 6.6: Fulfilment of list of requirements. (Continued)

E.3	The material(s) of the 3D-printed parts shall have similar dose attenuation properties as water.	Yes	
Standards requirements (F)			
F.1	The material(s) of the 3D-printed parts shall be biocompatible per ISO 10993-1:2018.	Yes	PA12 is biocompatible for applications with surface contact and limited duration (<24 h) conform EN ISO 10993-1:2018 [46].
Ergonomics requirements (G)			
G.1	The outer shape of the assembled applicator shall be conform the vaginal cavity.	Yes	
Safety requirements (H)			
H.1	The 3D-printed parts shall be able to be sterilised using an autoclave (134 °C, 3 minutes, 3.04 Bar) without being effected by the process.	Yes	A sterilisation report of a previous PA-12 applicator indicates that the print reaches 134 degrees within 4 minutes, which should be sufficient for sterilisation using an autoclave.
H.2	The design of the applicator shall ensure that the radioactive source shall never come in contact with the patient.	Yes	Fully enclosed 6F needle catheters will be used to guide the radioactive source through the applicator.
Installation, operation requirements (I)			
I.1	The applicator shall be able to be assembled inside the vaginal cavity of the patient.	Yes	
Wishes (J)			
J.1	The applicator should not need packing to be immobilised.	Concept 1: yes Concept 2: no	One radiotherapist-oncologist did not find it necessary to use packing to stabilise Concept 2. However, the other two radiotherapist-oncologists did find is necessary.
J.2	The applicator should contain an IC ring-structure.	Concept 1: yes Concept 2: no	

7

Discussion

The aim of this project was to develop and validate a design for a patient-tailored 3D-printed HDR BT applicator which features optimised interstitial needle channels based on the patient's anatomy and tumour location.

This chapter will discuss the used methods and the findings of different phases of the project. The chapter will conclude with recommendations for future designs of the personalised applicator designs.

7.1. Concept generation

During the conceptual design generation phase of the design process, brainstorming sessions were conducted with two people to generate solutions for the formulated how-to's. The limited number of people involved in the brainstorming sessions may have contributed to potential lack of incompleteness of the solutions generated.

7.2. Prototyping

The prototypes that were manufactured using SLS during both the prototyping and final design generation phase and for the user experience experiments indicate that the printing tolerance might have influenced some working principles of the prototypes. Specifically, the functionality of the snap-fit, the connection with the cervical stopper and the functioning of the needle lock holes were not consistent across the prototypes, although the same dimensions were used. An employee from Oceanz has indicated that the print direction (determined by the orientation of the model in the container) does significantly affect the dimensions of holes in the model. It is uncertain whether all prototypes were placed in the container with the same orientation. The orientation therefore may have affected the working principles of certain components in the prototypes.

7.3. Evaluation experiments

Dose attenuation properties of PA12

There are some differences in the measured dose of the 6 film segments, however they are irradiated with the irradiation plan. This could be due to small variations in the positioning of the six film segments within the test boxes: it is possible that not all film segments have been placed equally tightly alongside the source channel within the applicator, or that they might have shifted slightly upon closing the test boxes. This may have affected the calculated doses and therefore the percent-dose depth curves.

Workflow validation: delineation of structures in MIM

The Viomerse phantom does not feature a bowel, sigmoid and tumour. Therefore, these structures and the GTV, HR-CTV and IR-CTV were delineated in MIM using an anonymous patient case as reference and based on anatomical knowledge. The delineation process was not done following the correct delineation protocol as it was not done by a professional. The delineated structures were not checked by a professional. This may have resulted in the creation of an inaccurate mesh of the vaginal cavity and could have complicated the generation of needle channels and the creation of the applicator in SolidWorks.

Workflow validation: applicator model generation in Solidworks
During the generation of Concept 2 in SolidWorks, it became apparent that excessive smoothing had potentially been applied to the applicator mesh during the smoothing process in the Matlab code or that the vaginal cavity was not properly delineated in MIM: the proximal end of the ovoid tubes protruded from the dorsal side of the mesh, as is shown in Figure 7.1A. Figure 7.1B shows the small part that was added to the dorsal side of the mesh to guarantee that the ovoid tubes fit within the applicator geometry. However, this changed the fit of Concept 2 in comparison to Concept 1 which might have influenced the feedback obtained on Concept 2 during the user evaluation experiment.

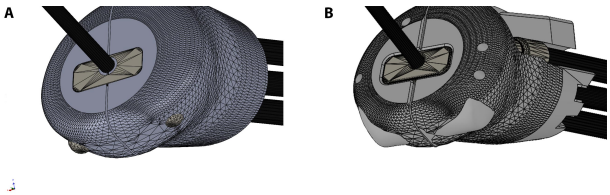


Figure 7.1: Screenshot of protruding ovoid tubes problem in Concept 2 during applicator model generation in Solidworks; (a) the protruding ovoid tubes; (b) the part that has been added to the mesh.

7.3.1. User experience experiment

Due to the adjusted radius of curvature of the guiding structures in the prototype of Concept 1 made for the user experience experiment, the guiding structures compressed the needle lock pins when inserted in the bracelet. Due to the compression of the pins, a considerable amount of force was needed to insert a needle through the pins and to rotate the pins to lock the needle. This not correctly functioning of the needle lock pins affected the provided feedback on Concept 1 during the user experience experiment.

Furthermore, the user experience experiment was conducted with less radiotherapist-oncologists than intended. Due to the summer vacation schedule of the radiotherapist-oncologists, the user evaluation experiment was conducted with three radiotherapist-oncologists instead of the initial idea of six. Hence, the amount of feedback was less than intended.

7.4. Future recommendations

Even though the two prototypes were received well by the three radiotherapist-oncologists, there are improvements to make. The following aspects are recommended for future development and/or research:

Future recommendations based on list of requirements

- **3D needle placement study:** in this report only a 2D needle placement option evaluation of the top of the personalised applicator is done (Section 6.2). However, to obtain a complete map of the needle reach in both concepts, a 3D study could be useful;
- **Compression and bending test**: to demonstrate the concepts' ability to withstand the forces exerted during insertion and removal of the applicator, and to validate the limits of PA12, a compression and bending test should be conducted;
- **MRI visibility test:** the validation of the personalised applicator's visibility and potential artefacts on MRI and CT images has not yet been conducted. Given that the personalised applicator designs include curved personalised needle channels, the reconstruction of needles might be more challenging compared to the current Geneva/Venezia applicators. An MRI visibility test will help validate if reconstruction of the applicator and the needle channels is possible.

Future design recommendations

- **Concept 1: adjust connection guiding structures to bracelet:** as stated earlier, in the prototype of Concept 1 used during the user experience experiment, the guiding structures compressed the needle lock pins when inserted in the bracelet. To prevent this from happening, the guiding structures should first extend perpendicularly from the bracelet before curving towards the entry region of the applicator;

- **Concept 1: needle lock pin insertion orientation indication on bracelet:** an indication on the bracelet regarding the insertion orientation of the needle lock pins should be added in order to avoid incorrect placement of the pins. For example, a small vertical extruded line could be added on the bracelet (since the needle lock pins need to be inserted in the bracelet with the flat part oriented vertically);
- **Concept 1: partly flatten handle for fixation clip:** in the final prototype, it was not possible to slide the fixation clip over the handles into the Geneva fixation element. Consequently, for instances where the handles need to be positioned higher due to needle channel placements, the top of the handles can be partly flattened. This would make it possible to slide the fixation clip over the handles in the fixation element;
- **Concept 1: remove spreading clip fixation:** attaching the spreading clip to the handle of the 3D-printed parts appeared unnecessary for their fixation. Therefore, handle's narrowing intended for this purpose can be removed;
- **Concept 2: improving the click system:** the click system to attach the 3D-printed parts to the ovoid tubes was was found to be insufficiently secure. One potential improvement could involve incorporating a snap-fit mechanism into this clicking system, thereby enhancing its overall security;

- **Concept 2: rounded edges at caudal and ventral position:** one of the three radiotherapist-oncologists pointed out that the sharp edges at the caudal and ventral positions of Concept 2 might cause injury during insertion and removal of the applicator. In the prototype, these edges were rounded by 1mm. For future designs, it is recommended to increase the size of this rounding or to make this element also conform the mesh of the patient's vaginal cavity;
- **Concept 1 and 2: include patient ID on 3D-print:** to minimise the possibility of placing the incorrect personalised applicator, the patient ID should be displayed on the applicators. For example, in Concept 1, the ID could be printed as an extrusion on the handle and in Concept 2, it could be printed debossed on the median plane.

Other recommendations

- **More research regarding cleaning of the needle channels:** in the two designs it is feasible to place 6F needles through the designated IS needle channels. However, in one Concept 1 prototype, it was not possible to properly clean one of the two IC ring channels. This could possible be attributed to the heating process during SLS printing: the SLS technique uses heat, which can lead to shrinkage of the printed product [54]. The thicker the wall in the model, the more heat is generated in the printing process, increasing the risk that the needle channel becomes smaller than designed, which makes it harder to remove the uncured powder from the channel after cooling. Moreover, the feedback received during the user experience experiment indicates that the needles still encounter substantial friction during insertion in Concept 1. Hence, to ensure needle accessibility and to reduce the friction during needle insertion in the channels, it is desired to explore options for cleaning and enhancing the internal smoothness of the channels;

- **Production, post-processing and delivery time of the applicator:** a validation test run needs to be conducted with Oceanz to assess whether printing and post-processing the applicators can be accomplished within the intended timeframe (Thursday to Tuesday).

As it was not part of the scope of the project, no attention was paid on needle insertion accuracy. However, the following needle insertion aspects are recommended for future development and/or research:

- **Needle channels ends perpendicular to tissue:** one of the three radiotherapist-oncologists stated that due to the fact that the needles do not always exit the applicator at a perpendicular angle to the tissue, the needle might slide along the tissue instead of penetrating trough it when inserted. To prevent this and to improve the designs, the needle exits should be oriented perpendicular to the tissue;
- **Tapered IS needle channel ends:** by tapering the IS needle channel ends, needle protrusion and angle accuracy will be increased since the needle will have less space to move. However, it is worth noting that tapering the IS needle ends will probably make the cleaning of the channels more challenging;

8

Conclusion

The goal of this project was to develop and validate a complete and feasible embodiment design for a 3D-printed HDR BT applicator with a custom vaginal topography and optimised needle channels, based on the patient's anatomy and tumour location. This report shows the design process, prototyping and evaluation of two conceptual designs.

It has been validated that the the workflow for generating the two proposed conceptual designs is feasible and that both designs can be manufactured in PA12 using SLS printing technique. In addition, the conducted dose attenuation experiment indicate that PA12 has water-equivalent attenuation properties, thus making it suitable as a material for the applicator. The outcome of the needle planning options validation suggest that the top of Concept 1 provides more space for personalised needle channels. Three radiotherapist-oncologists validated the usability of both conceptual designs. Although not all design elements worked correctly, the prototypes were well received.

It can be concluded that two 3D-printed HDR BT applicator designs have been developed, produced and validated. Of these two concepts, Concept 1 shows the most promise to be used as a design for a patient-tailored 3D printed BT applicator. However, to ensure the proper functioning of the working principles, further development is required. If the recommended improvements are implemented, the design has the potential to be used as applicator in the treatment of cervical cancer.

Bibliography

[1] Hyuna Sung et al. “Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries”. In: *CA: a cancer journal for clinicians* 71.3 (2021), pp. 209–249.

[2] Susanna I Lee and Mostafa Atri. “2018 FIGO staging system for uterine cervical cancer: enter cross-sectional imaging”. In: *Radiology* 292.1 (2019), pp. 15–24.

[3] Pushpa Naga Ch et al. “The management of locally advanced cervical cancer”. In: *Current opinion in oncology* 30.5 (2018), pp. 323–329.

[4] Huijun Chen et al. “Clinical efficacy of modified preoperative neoadjuvant chemotherapy in the treatment of locally advanced (stage IB2 to IIB) cervical cancer: a randomized study”. In: *Gynecologic oncology* 110.3 (2008), pp. 308–315.

[5] Robyn Banerjee and Mitchell Kamrava. “Brachytherapy in the treatment of cervical cancer: a review”. In: *International journal of women’s health* 6 (2014), p. 555.

[6] Gerald E Hanks, David F Herring, and Simon Kramer. “Patterns of care outcome studies results of the national practice in cancer of the cervix”. In: *Cancer* 51.5 (1983), pp. 959–967.

[7] Kathy Han et al. “Trends in the utilization of brachytherapy in cervical cancer in the United States”. In: *International Journal of Radiation Oncology* Biology* Physics* 87.1 (2013), pp. 111–119.

[8] Monica Serban et al. “Characterization of combined intracavitary/interstitial brachytherapy including oblique needles in locally advanced cervix cancer”. In: *Brachytherapy* 20.4 (2021), pp. 796–806.

[9] Ankur Mourya, Lalit Mohan Aggarwal, and Sunil Choudhary. “Evolution of brachytherapy applicators for the treatment of cervical cancer”. In: *Journal of Medical Physics* 46.4 (2021), p. 231.

[10] University of Health Network. *What to Expect When Getting High-Dose Rate (HDR) Brachytherapy to the Esophagus*. Oct. 2019. URL: https://www.uhn.ca/PatientsFamilies/Health_Information/Health_Topics/Documents/High_Dose_Rate_Brachytherapy_Gynecological_Cancer.pdf#search=HDR%5C%20brachytherapy.

[11] Franziska Walter et al. “Combined intracavitary and interstitial brachytherapy of cervical cancer using the novel hybrid applicator Venezia: Clinical feasibility and initial results”. In: *Brachytherapy* 17.5 (2018), pp. 775–781.

[12] Richard Pötter et al. “Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer”. In: *Radiotherapy and oncology* 83.2 (2007), pp. 148–155.

[13] Li-Min Sun et al. “Computer tomography-assisted three-dimensional technique to assess rectal and bladder wall dose in intracavitary brachytherapy for uterine cervical cancer”. In: *Radiotherapy and oncology* 71.3 (2004), pp. 333–337.

[14] Matthew M Harkenrider et al. “Image-based brachytherapy for the treatment of cervical cancer”. In: *International Journal of Radiation Oncology* Biology* Physics* 92.4 (2015), pp. 921–934.

[15] Jacob C Lindegaard et al. “MRI-guided 3D optimization significantly improves DVH parameters of pulsed-dose-rate brachytherapy in locally advanced cervical cancer”. In: *International Journal of Radiation Oncology* Biology* Physics* 71.3 (2008), pp. 756–764.

[16] Henrike Westerveld et al. “Image-guided adaptive brachytherapy (IGABT) for primary vaginal cancer: results of the International Multicenter RetroEMBRAVE Cohort Study”. In: *Cancers* 13.6 (2021), p. 1459.

[17] Christine Haie-Meder et al. “Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group□(I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV”. In: *Radiotherapy and oncology* 74.3 (2005), pp. 235–245.

[18] Jamema Swamidas and Umesh Mahantshetty. “ICRU report 89: prescribing, recording, and reporting brachytherapy for cancer of the cervix”. In: *Journal of Medical Physics* 42.suppl. 1 (2017), p. 48.

[19] Richard Pötter et al. “Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy—3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology”. In: *Radiotherapy and oncology* 78.1 (2006), pp. 67–77.

[20] Akila N Viswanathan, Bruce Thomadsen, American Brachytherapy Society Cervical Cancer Recommendations Committee, et al. “American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: general principles”. In: *Brachytherapy* 11.1 (2012), pp. 33–46.

[21] Akila N Viswanathan et al. “American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: high-dose-rate brachytherapy”. In: *Brachytherapy* 11.1 (2012), pp. 47–52.

[22] Bastien Rigaud et al. “Modeling complex deformations of the sigmoid colon between external beam radiation therapy and brachytherapy images of cervical cancer”. In: *International Journal of Radiation Oncology* Biology* Physics* 106.5 (2020), pp. 1084–1094.

[23] Elekta Group. *Applicator Guide*. 2020. URL: https://www.elekta.com/products/brachytherapy/documents/Brachytherapy-Applicator-Guide.pdf.

[24] Rianne C Laan et al. “MRI-driven design of customised 3D printed gynaecological brachytherapy applicators with curved needle channels”. In: *3D printing in medicine* 5.1 (2019), pp. 1–8.

[25] Norbert FM Roozenburg and Johannes Eekels. *Product design: fundamentals and methods*. Wiley, 1995.

[26] Annemiek Van Boeijen et al. *Delft design guide: Design strategies and methods*. 2014.

[27] James J Sohn et al. “A Novel Workflow with a Customizable 3D Printed Vaginal Template and a Direction Modulated Brachytherapy (DMBT) Tandem Applicator for Adaptive Interstitial Brachytherapy of the Cervix”. In: *Journal of Clinical Medicine* 11.23 (2022), p. 6989.

[28] Elekta. *Geneva instructions for use*. 2020.

[29] Elekta. *Applicator Guide Brachytherapy Applicators*. 2020.

[30] Elekta. *Advanced Gynecological Applicator, Instructions for Use for: 3905TH*. 2019.

[31] Aime M Gloi. “First clinical implementation of the Capri applicator”. In: *Journal of Applied Clinical Medical Physics* 15.1 (2014), pp. 386–394.

[32] Sanna Nilsson et al. “A unique approach to high-dose-rate vaginal mold brachytherapy of gynecologic malignancies”. In: *Brachytherapy* 14.2 (2015), pp. 267–272.

[33] Monica Serban et al. “Characterization of combined intracavitary/interstitial brachytherapy including oblique needles in locally advanced cervix cancer”. In: *Brachytherapy* 20.4 (2021), pp. 796–806.

[34] Eckert Ziegler. *Tulip Applicator Family*. 2020.

[35] Mallika Marar et al. “Applying 3D-printed templates in high-dose-rate brachytherapy for cervix cancer: simplified needle insertion for optimized dosimetry”. In: *International Journal of Radiation Oncology* Biology* Physics* 114.1 (2022), pp. 111–119.

[36] Ericka Wiebe et al. “Customized vaginal vault brachytherapy with computed tomography imaging-derived applicator prototyping”. In: *Brachytherapy* 14.3 (2015), pp. 380–384.

[37] Antonio L Damato, Robert A Cormack, and Akila N Viswanathan. “A novel intracavitary applicator design for the treatment of deep vaginal fornices: preliminary dose metrics and geometric analysis”. In: *Journal of Contemporary Brachytherapy* 7.1 (2015), pp. 48–54.

[38] European Parliament. “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”. In: *Official Journal of the European Union* 60.L117 (2017), pp. 1–175.

[39] ISO 14971. *Medical devices - Application of risk management to medical devices*. 2019.

[40] ISO/TR 24971. *Medical devices - Guidance on the application of ISO 14971*. 2020.

[41] Joel Poder et al. “A risk-based approach to development of ultrasound-based high-dose-rate prostate brachytherapy quality management”. In: *Brachytherapy* 17.5 (2018), pp. 788–793.

[42] Shada Wadi-Ramahi et al. “Failure modes and effects analysis in image-guided high-dose-rate brachytherapy: Quality control optimization to reduce errors in treatment volume”. In: *Brachytherapy* 15.5 (2016), pp. 669–678.

[43] D Allan Wilkinson and Matthew D Kolar. “Failure modes and effects analysis applied to high-dose-rate brachytherapy treatment planning”. In: *Brachytherapy* 12.4 (2013), pp. 382–386.

[44] S Pugh. *Total Design: Integrated methods for succesful product engineering.* Wokingham: Addison-Wesley, 1961.

[45] ISO/IEC Directives. *Principles and rules for the structure and drafting of ISO and IEC documents*. 2018.

[46] Oceanz B.V. *Oceanz PA12*. URL: https://www.oceanz.eu/en/materials/oceanz-pa12/.

[47] Oceanz B.V. *Vapor Polish*. URL: https://www.oceanz.eu/nabehandeling/vapor-polish/?_gl=1*wk7yr5*_up*MQ..*_ga*MTcyNjMxNzgxLjE2ODY1NzY5MDc.*_ga_MG18M9C68S*MTY4NjU3NjkwNi4xLjEuMTY4NjU3Njk4Mi4wLjAuMA..*_ga_81RKW0M78Q*MTY4NjU3NjkwNi4xLjEuMTY4NjU3Njk4Mi4wLjAuMA..

[48] Ravinder Nath et al. “Dosimetry of interstitial brachytherapy sources: recommendations of the AAPM Radiation Therapy Committee Task Group No. 43”. In: *Medical physics* 22.2 (1995), pp. 209–234.

[49] J Adam M Cunha et al. “Evaluation of PC-ISO for customized, 3D printed, gynecologic HDR brachytherapy applicators”. In: *Journal of applied clinical medical physics* 16.1 (2015), pp. 246–253.

[50] Benjamin D Harris, Sanna Nilsson, and Christopher M Poole. “A feasibility study for using ABS plastic and a low-cost 3D printer for patient-specific brachytherapy mould design”. In: *Australasian physical & engineering sciences in medicine* 38 (2015), pp. 399–412.

[51] Oceanz B.V. *Oceanz PA12 General Design Guidelines*. URL: https://www.oceanz.eu/app/uploads/2022/06/Oceanz_PA12_General_Design-guidelines.pdf.

[52] John Brooke. “Sus: a “quick and dirty’usability”. In: *Usability evaluation in industry* 189.3 (1996), pp. 189–194.

[53] Elekta. *Martinez Prostate Template Set Instructions for Use*. 2016.

[54] Oceanz B.V. *Features and facts about the SLS Technology*. URL: https://www.oceanz.eu/blog/features-and-facts-about-the-sls-technology/.

[55] Witold Jamróz et al. “3D printing in pharmaceutical and medical applications–recent achievements and challenges”. In: *Pharmaceutical research* 35 (2018), pp. 1–22.

A

Literature review results

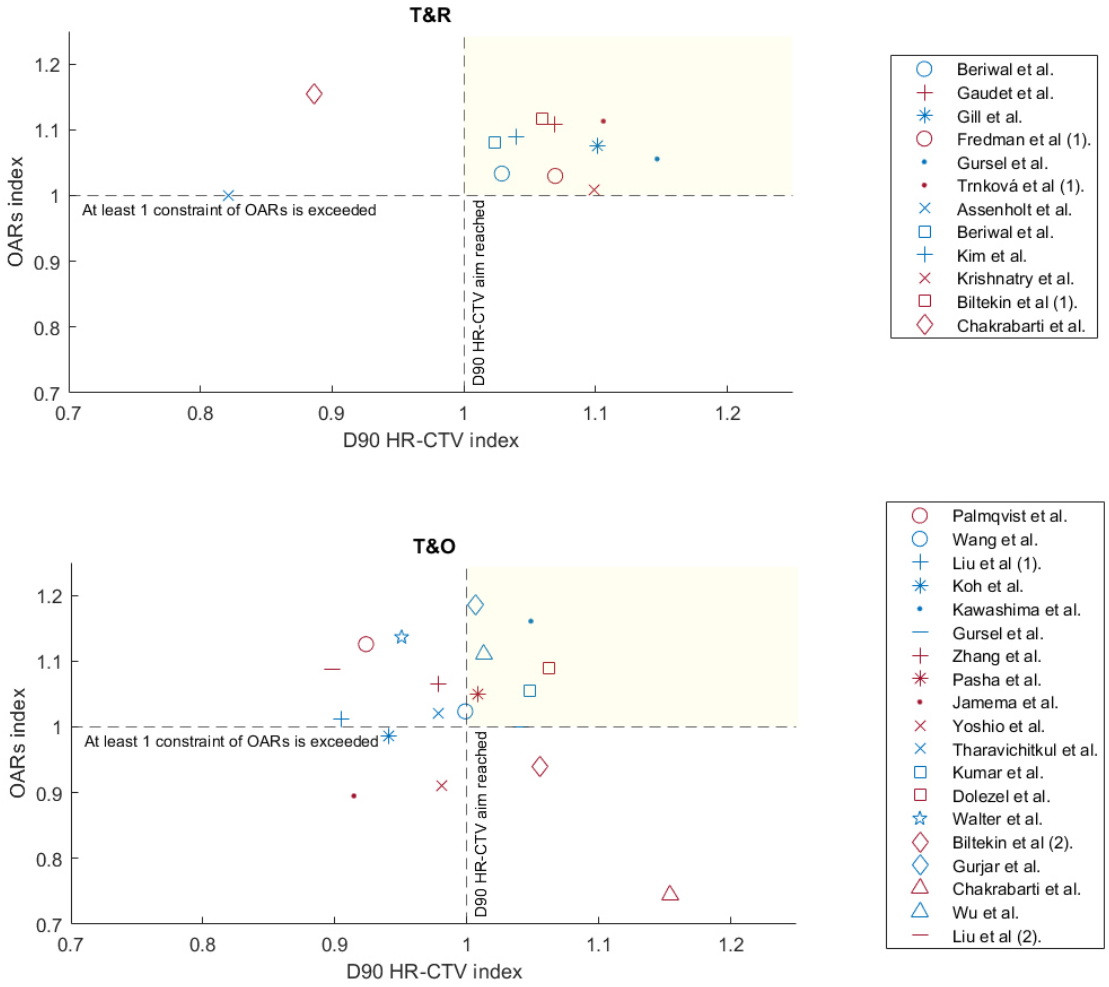


Figure A.1: D_{90} HR-CTV index versus OARs index per study that uses a T&R or T&O applicator. When studies met their D_{90} HR-CTV planning aims and did not exceed one of their OARs constraints, the studies are positioned in the 'golden corner'.

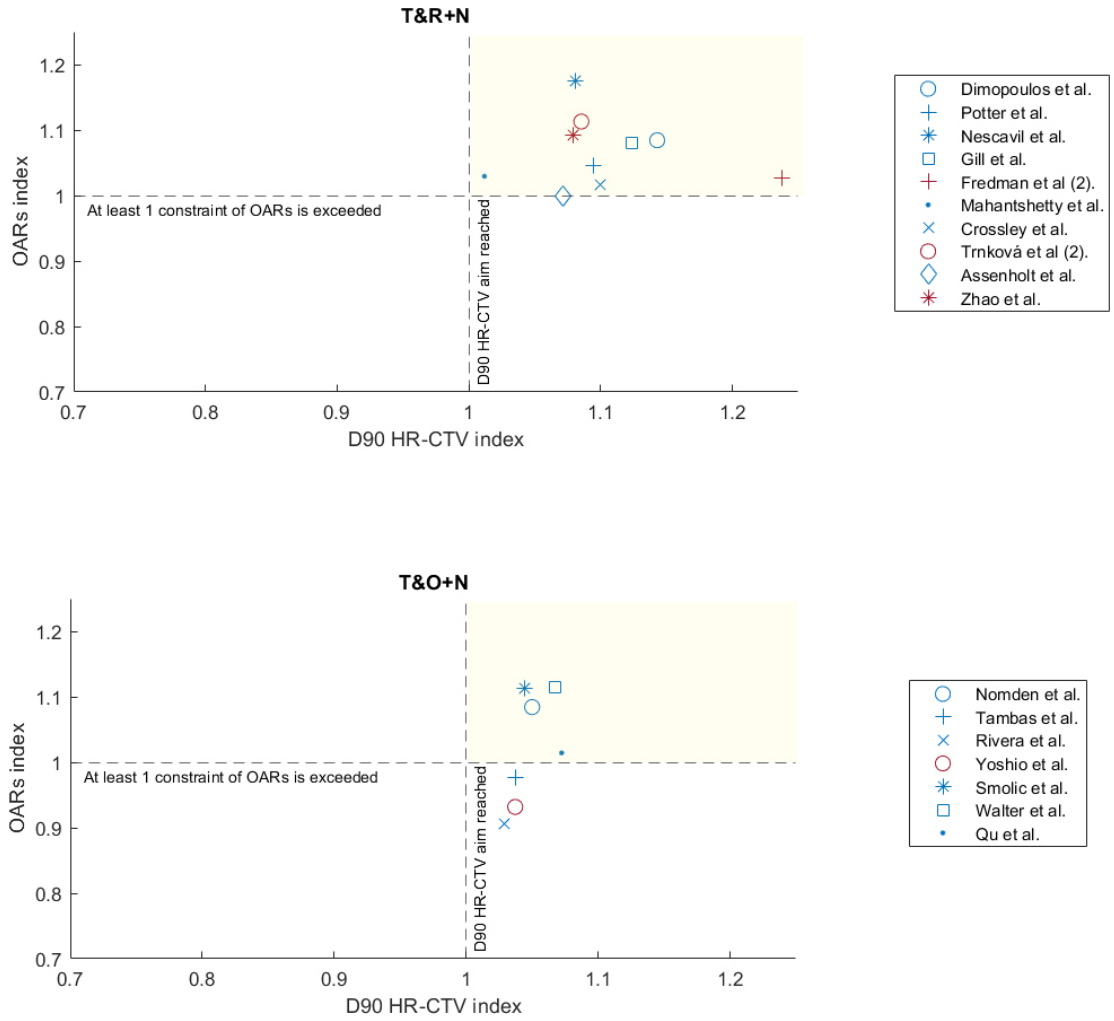


Figure A.2: D_{90} HR-CTV index versus OARs index per study that uses a T&R+N or T&O+N applicator. When studies met their D_{90} HR-CTV planning aims and did not exceed one of their OARs constraints, the studies are positioned in the 'golden corner'.

B

Current applicator types analysis

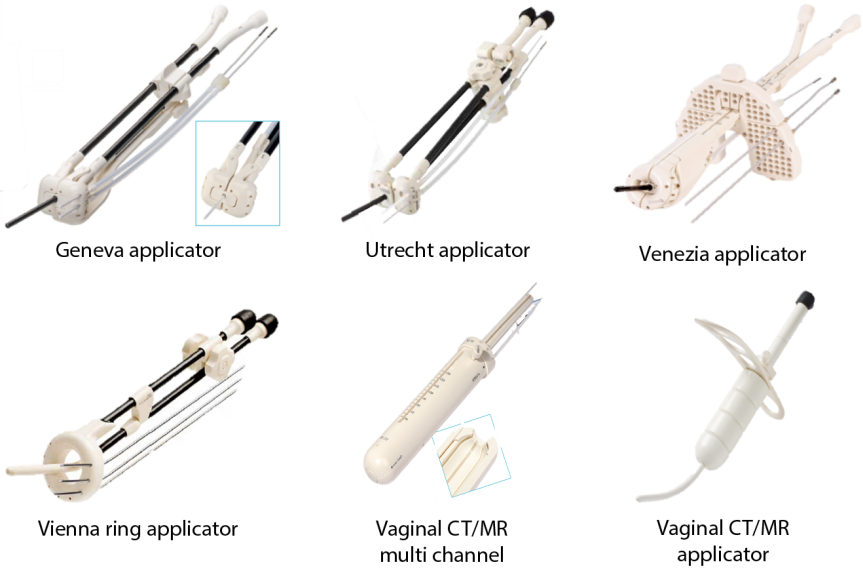


Figure B.1: The standard applicators that are included in the analysis. FLTR top: Geneva applicator [28], Utrecht applicator [29], Venezia applicator [30]. Bottom: Vienna ring applicator [29], Vaginal CT/MR multi channel [29], Vaginal CT/MR applicator [29].

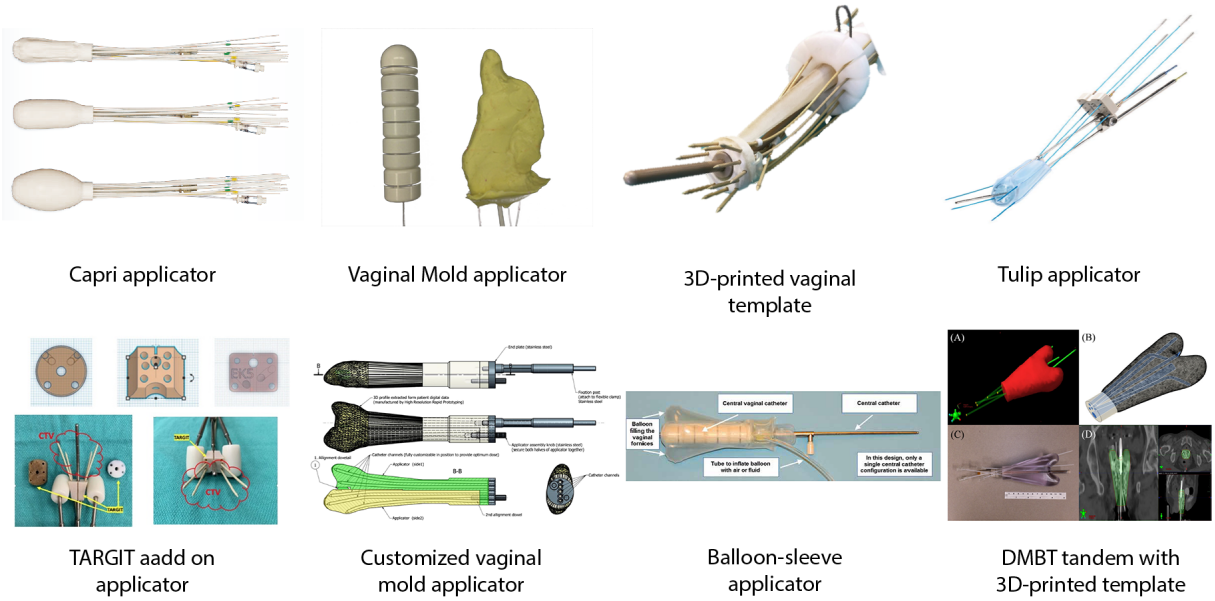


Figure B.2: The experimental applicators that are included in the analysis. FLTR top: Capri applicator [31], Vaginal mold [32], 3D-printed vaginal template applicator [33], Tulip applicator [34]. Bottom: TARGIT applicator [35], Customized vaginal mold applicator [36], Balloon-sleeve applicator [37], DMBT tandem with 3D-printed template [27].

C

Process tree analysis

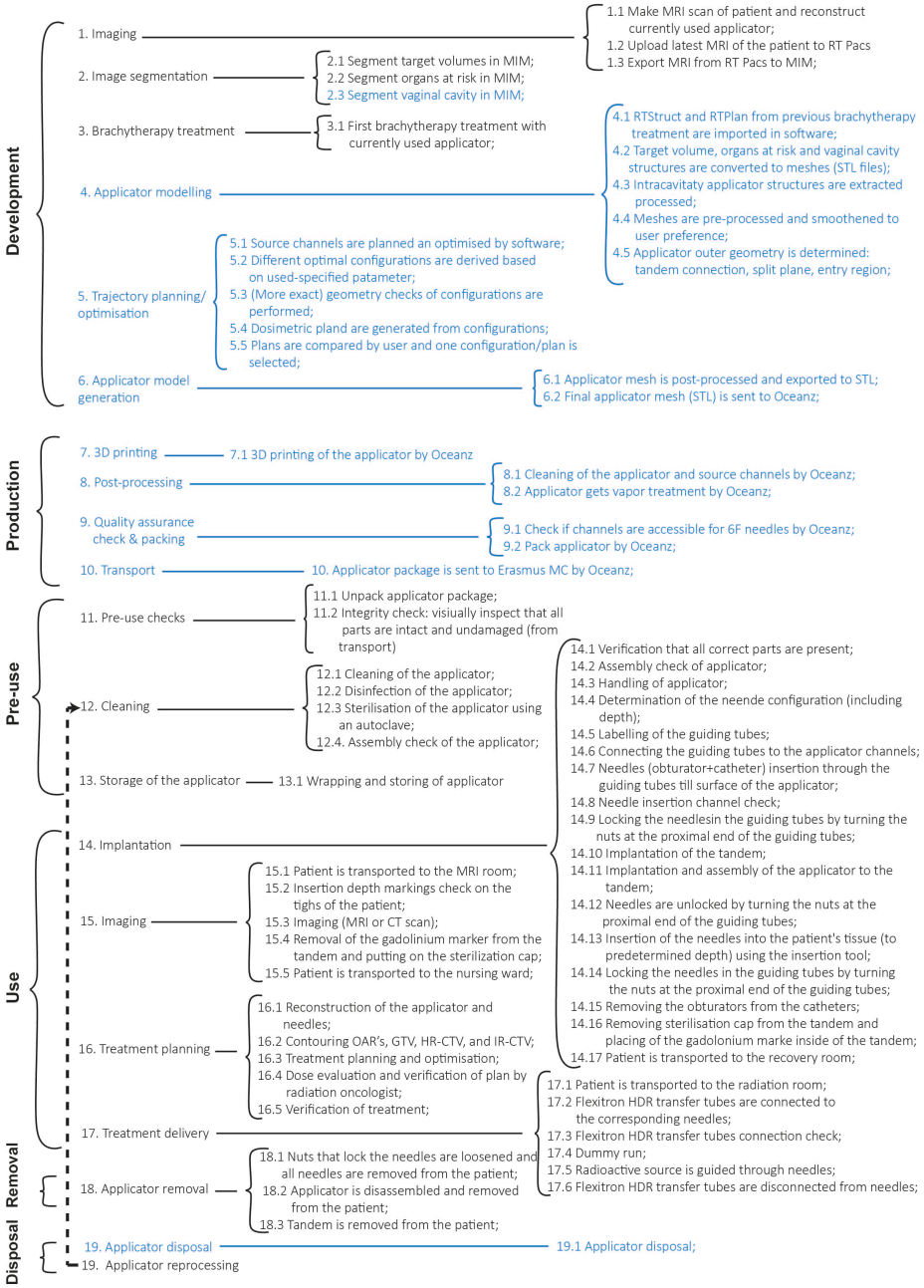


Figure C.1: Process tree of an applicator for HDR BT treatment for cervical cancer in Erasmus MC, from the development phase of the personalised applicator till the disposal phase. The black steps are for both the currently used applicator and the new 3D printed applicator, the blue steps represent steps that will only be necessary using the new 3D printed applicator.

D

Risk analysis

Expected workflow ARCHITECT applicator risk analysis: misuse

	5.4: Identification of hazards and hazardous situation								5.5: Risk evaluation				7.1: Risk control option analysis					
Overall process step	**Step Name**	**Step NR**	**What/how description**	**Misuse description**	**Foreseeable sequence of events**	**Hazard**	**Risk NR**	**Hazardous situation(s)**	**Harm**	**Severity**	**Probability**	**Acceptable?**	**Current process control**	**Risk control option**	**Risk control measure**	**Severity**	**Probability**	**Acceptable?**
First application brachytherapy treatment	**1. Imaging**	1.1	Make MRI scan and reconstruct standard applicator	New applicator design is based on malplaced applicator in previous application (PU)	I. Standard applicator is not placed correctly (e.g. tandem perforation) II. Shifted applicator before or during imaging III. Shifted applicator not recognised during reconstruction IV. New applicator design based on shifted applicator V. New applicator cannot be inserted properly	Functionality - incorrect measurements	R1	Failure to implant the applicator	Painful insertion for the patient Treatment delay	2	2	Investigate further risk control	None	3	Provide instructions to always check reconstruction;	2	1	Yes
				New applicator design is based on not a properly reconstructed applicator (PU)	I. Applicator reconstruction is incorrect II. New applicator design based on shifted applicator III. New applicator cannot be inserted properly	Functionality - incorrect measurements	R2	Failure to implant the applicator	Painful insertion for the patient Treatment delay	2	2	Investigate further risk control	None	3	Provide instructions to always check reconstruction;	2	1	Yes
				Tandem or applicator size ill-chosen for patient (PU)	I. Applicator reconstruction shows that a different tandem angle / length or applicator size was more appropriate II. New applicator design based on old applicator III. Critical organs / target structures are not optimally displaced / positioned IV. Patient is irradiated with non-optimal dose distribution	Radiation energy - ionising radiation	R3	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	4	Investigate further risk control	None	3	Provide instructions that in case of non-optimal applicator choice, the patient is not treated with the patient-tailored applicator in next application	2	2	Yes
		1.2	Upload MRI of the patient from last brachy treatment to RT Pacs															
		1.3	Export MRI from RT Pacs to MIM															
	2. Image segmentation	2.1	Segment target volumes in MIM	Applicator is used outside of intended purpose (IU)	I. Target volume segmentation shows target region that is not within intended use II. New applicator is nevertheless indicated III. Patient is irradiated with non-optimal dose distribution	Radiation energy - ionising radiation	R4	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	4	Investigate further risk control	None	3	Provide instructions on which patient-groups to be included. Software provides warning when dose constraints are exceeded	2	2	Yes
		2.2	Segment organs at risk in MIM															
		2.3	Segment vaginal cavity in MIM	Vaginal cavity incorrectly contoured (PU)	I. Incorrect contouring of vaginal cavity II. New applicator cannot be inserted properly	Functionality - incorrect measurements	R5	Failure to implant the applicator	Painful insertion for the patient Treatment delay	2	5	Investigate further risk control	None	3	Provide clear instructions and training on contouring the vaginal cavity	2	3	Yes
	3. Brachytherapy treatment	3.1	First brachytherapy treatment with currently used applicator															
New applicator design	**4. Applicator modelling**	4.1	Previously used RTStruct and RTPlan are imported in software	Data is imported from the wrong patient (mistake patient ID) (PU)	I. Applicator does not match the geometry of vaginal cavity of the patient's the CT/MRI scan; II. Applicator is printed with incorrect geometry; III. New applicator cannot be inserted properly	Functionality - incorrect measurements	R6	Failure to implant the applicator	Painful insertion for the patient Treatment delay	2	2	Insignificant or negligible risk	None	2	Software asks user to confirm anonymised patient ID	2	1	Yes
		4.2	Target volume, organs at risk and vaginal cavity structures are converted to meshes (STL files)	Give name to STL files other than prespecified / mix up names of structures (PU)	I. Name of meshes is different than prespecified in list of wildcards II. Structure is not found in software III. Applicator cannot be generated I. Name of meshes is mixed up II. Source channels are not optimal III. Dose distrbution still passes constraints IV. Patient is irradiated with non-optimal dose distribution	Radiation energy - ionising radiation	R7	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	3	Investigate further risk control	None	3	Software indicates which structure is which (name on screen + colour indication)	2	1	Yes
		4.3	Intracavitary applicator structures are extracted and processed	Intracavitary structure is not contained within vaginal cavity segmentation (PU)	I. Incorrect contouring of vaginal cavity II. Existing applicator structures cannot be properly integrated in design III. Applicator mesh still passes quality checks IV. Integrity of needle or source channels is compromised V. Applicator is used without all possible needles / IC structures	Radiation energy - ionising radiation	R8	Treatment plan non-optimal	Excessive irradiation of healthy tissue or tumour	3	3	Investigate further risk control	None	1	Software adds a buffer around intracavitary structures such that these can always be integrated	3	2	Yes
		4.4	Meshes are pre-processed and smoothened to user preference	User applies too much or too little smoothing on mesh (PU)	I. Applicator mesh contains rough edges or does not match geometry of vaginal cavity; II. Applicator is printed with incorrect geometry; III. New applicator cannot be inserted properly / Sharp edges causes discomfort to the patient during insertion	Functionality - sharp interface Functionality - incorrect measurements	R9	Outer surface of applicator contains sharp edges / Failure to implant the applicator	Painful insertion for the patient Treatment delay	2	3	Investigate further risk control	None	2	Software shows the result of different smoothing settings, after which user has to confirm	2	1	Yes

		4.5	Applicator outer geometry is determined: tandem connection, split plane, entry region	User determines entry plane at a too low height (PU)	I. Applicator mesh is generated II. Insertion of the applicator leads to pain at the introitus;	Functionality - incorrect measurements	R10	Failure to implant the applicator	Painful insertion for the patient Treatment delay	2	1	Insignificant or negligible risk	None	2	Software performs automatic entry plane determination and lets user check	2	1	Yes
	5. Trajectory planning/optimisation	5.1	Source channels are planned and optimised	Local curvature constraints of source channels are exceeded (PU)	I. User tests limits of curvature constraints / needle angles II. Applicator is printed with channels that are not accessible for source cable / needles III. Needles cannot be inserted or IC structure cannot be connected IV. Applicator is used without all possible needles / IC structures	Radiation energy - ionising radiation	R11	Treatment plan non-optimal	Excessive irradiation of healthy tissue of tumour	3	1	Insignificant or negligible risk	None	1	Make constraints on curvature and needle angles read-only	3	1	Yes
		5.2	Different optimal configurations are derived based on user-specified parameter	User-specified parameter (coverage radius) defined to be too large (PU)	I. User uses too large value for coverage radius II. User chooses plan with least needles but non-optimal dose distribution III. Dose distribution still passes constraints IV. Patient is irradiated with non-optimal dose distribution	Radiation energy - ionising radiation	R12	Treatment plan non-optimal	Slight overirradiation or healthy tissue or underdosage of tumour	2	2	Investigate further risk control	None	3	Software indicates standard range for user parameters coverage radius, informs about other plans	2	1	Yes
		5.3	(More exact) Geometry checks of configurations are performed	User selects different parameters for instrumentation used (PU)	I. User specifies different dimensions for needles, tandem, guiding tubes, etc. than conventional II. Generated channels intersect or are ill-positioned III. Needles cannot be inserted or IC structure cannot be connected IV. Applicator is used without all possible needles / IC structures	Radiation energy - ionising radiation	R13	Treatment plan non-optimal	Excessive irradiation of healthy tissue or tumour	3	1	Insignificant or negligible risk	None	1	Make instrumentation parameters read-only	3	1	Yes
		5.4	Dosimetric plans are generated from configurations															
		5.5	Plans are compared by user and one configuration/plan is selected	User selects plan that is objectively not optimal for a non-valid reason (PU)	I. User chooses plan with non-optimal dose distribution II. Dose distribution still passes constraints III. Patient is irradiated with non-optimal dose distribution	Radiation energy - ionising radiation	R14	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	5	Investigate further risk control	None	3	Software informs about other plans, asks user to confirm whether to select an objectively worse plan	2	3	Yes
	6. Applicator model generation	6.1	Applicator mesh is post-processed and exported to STL	Applicator smoothing settings are set too coarse (PU)	I. Applicator is printed with coarse geometry; II. New applicator cannot be inserted properly.	Functionality - incorrect measurements	R15	Failure to implant the applicator	Painful insertion for the patient Treatment delay	2	3	Investigate further risk control	None	2	Software warns about coarseness of outer applicator surface using a metric	2	1	Yes
		6.2	Final applicator mesh (STL) is sent to Oceanz															
Manufacturing	**7. 3D printing**	7.1	3D printing of the applicator by Oceanz															
	8. Post-processing	8.1	Cleaning of the applicator and source channels by Oceanz															
		8.2	Applicator gets vapor treatment by Oceanz															
	9. Quality assurance check & packing	9.1	Checking if channels are accessible for 6F needles by Oceanz															
		9.2	Packing of applicator by Oceanz															
Transport	**10. Transport**	10.1	Applicator package is sent to Erasmus MC by Oceanz	Applicator package was sent late (US)	I. Applicator package is delayed; II. Personalised applicator cannot be used during treatment; III. Another applicator is used; IV. Patient is irradiated with non-optimal dose distribution or treatment delay.	Radiation energy - ionising radiation	R16	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour Treatment delay	2	2	Investigate further risk control	None	3	Introduce guidelines on when to deliver the STL files, when to print the applicator and when it should be send at the latest	2	2	**Yes**
Pre-use	**11. Pre-use checks**	11.1	Unpack applicator package	Sharp tools are used for unpacking the applicator (EQ)	I. Applicator is damaged by sharp tool during unpacking; II. Applicator contains sharp edges; III. Sharp edges may causes discomfort to the patient during insertion.	Functionality - sharp interface	R17	Outer surface of applicator contains sharp edges	Discomfort or pain to patient by insertion	1	1	Insignificant or negligible risk	Warning in applicator manual and protocol	3				
		11.2	Integrity check: visually inspect that all parts are delivered intact and undamaged (from transport)	Check is not done properly (PU)	I. Not noted that the applicator is damaged; II. Applicator may break during insertion or may contains sharp edges; III. Sharp edges may causes discomfort to the patient during insertion.	Functionality - sharp interface	R18	Outer surface of applicator contains sharp edges	Discomfort or pain to patient by insertion	1	1	Insignificant or negligible risk	Warning in applicator manual and protocol	3				
	12. Cleaning, disinfection and sterilisation of the applicator	12.1	Cleaning of the applicator	Applicator is not properly cleaned (PU)	I. Uncured powder remains in the channels after manufacturing; II. Applicator channels can therefore not properly be rinsed/cleaned; III. Needles carry uncured powder during insertion; IV. Uncured powder comes into contact with patient tissue.	Chemical - particles	R19	PA-12 powder comes into contact with patient tissue	Acute reactions / toxicity	3	2	Investigate further risk control	Warning in applicator manual and protocol	1	Needle channel constraints (length-diameter ratio, curvature) and optimising cleaning tools	3	1	Yes
				CSA department has no time to clean the applicator before the day of treatment (PU)	I. Applicator is not cleaned, disinfected and sterilised before the day of treatment; II. Applicator can not be used during treatment; IV. Another applicator is used; V. Patient is irradiated with non-optimal dose distribution.	Radiation energy - ionising radiation	R20	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour Treatment delay	2	3	Investigate further risk control	None	3	Introduce guidelines on which day the applicator should be cleaned at the latest	2	3	**Yes**

		12.2	Disinfection of the applicator	Applicator is not properly disinfected (PU)	I. Applicator is contaminated between unpacking and cleaning II. Applicator is not properly disinfected; III. Applicator introduces pathogenic organisms to patient tissue.	Biological agents - bacteria/viruses	R21	Organisms introduced into patient tissue	Bacterial or viral infection	3	2	Investigate further risk control	Warning in applicator manual and protocol	1	Needle channel constraints (length-diameter ratio, curvature)	3	1	Yes
		12.3	Sterilisation of the applicator using an autoclave	Applicator is not properly sterilised (PU)	I. Applicator is contaminated between unpacking and cleaning II. Applicator is not properly sterilised; III. Applicator introduces pathogenic organisms to patient tissue.	Biological agents - bacteria/viruses	R22	Organisms introduced into patient tissue	Bacterial or viral infection	3	2	Investigate further risk control	Warning in applicator manual and protocol	1	Needle channel constraints (length-diameter ratio, curvature), establish design specifications that secure sterilisation ability	3	1	Yes
		12.4	Assembly check of applicator	Applicator is affected by cleaning processes (PU)	I. The needle guidance channel(s) are affected by cleaning processes; II. Needle guiding channels/IC structures are not accessible for catheters anymore; III. Applicator is used without all possible needles / IC structures or another applicator is used for treatment.	Radiation energy - ionising radiation	R23	Treatment plan non-optimal	Excessive irradiation of healthy tissue of tumour	3	1	Insignificant or negligible risk	Warning in applicator manual and protocol	1				
	13. Storage of the applicator	13.1	Wrapping and storing applicator															
Second application brachytherapy treatment	**14. Implantation of the applicator**	14.1	Verification that all correct parts are present	Applicator of other patient is opened/used (EQ)	I. Applicator from other patient is unpacked in OR; II. Wrong applicator is used during treatment; III. Incorrect dwell positions.	Funcitonality - incorrect applicator	R24	Treatment plan non-optimal	Excessive irradiation of healthy tissue of tumour	3	1	Insignificant or negligible risk	Warning in applicator manual and protocol	3				
		14.2	Assembly check of applicator															
		14.3	Handling of applicator	Applicator is dropped (PU)	I. Applicator hits the ground; II. Integrity of needle or source channels is compromised; III. Needles cannot be inserted or IC structure cannot be connected IV. Applicator is used without all possible needles / IC structures	Radiation energy - ionising radiation	R25	Treatment plan non-optimal	Excessive irradiation of healthy tissue or tumour	3	1	Insignificant or negligible risk	Warning in applicator manual and protocol	3				
		14.4	Determination of needle configuration (including depth)	Needle insertion depth is misinterpreted / needles are interchanged (PU)	I. Incorrect needle insertion depth is determined from preplan; II. Needles are inserted with incorrect depth; III. Incorrect dwell positions.	Radiation energy - ionising radiation Functionality - sharp interface	R26	Needle tip inserted not on planned depth	Excessive irradiation of healthy tissue or tumour	3	3	Investigate further risk control	Needle insertion depth check and warning in applicator manual	3	Provide clear instructions and interface of preplan to read out needle insertion depth	3	1	Yes
				An extra needle needs to be inserted (US)	I. No needle channel made for extra needle; II. Extra needle must be inserted by hand with image guidance; III. Non-optimal needle placement; IV.Patient is irradiated with non-optimal dose distribution	Radiation energy - ionising radiation Functionality - free needle placement	R27	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	2	Investigate further risk control	None	1 and 3	Design interface which makes guidance of an extra free placed needle possible	2	1	Yes
		14.5	Labelling of the guiding tubes															
		14.6	Connecting the guiding tubes to the applicator channels	Labelled guiding tubes are not connected to corresponing channel (channel mix up) (PU)	I. Needles are inserted in wrong channel; II. Needles are inserted with incorrect depth; III. Incorrect dwell positions.	Radiation energy - ionising radiation	R28	Needle tip inserted not on planned depth	Excessive irradiation of healthy tissue or tumour	3	2	Investigate further risk control	Needle insertion depth check and warning in applicator manual	2 and 3	Design interface as such that guiding tube are sorted (bracelet) + provide clear instructions on checking guiding tubes	3	1	Yes
		14.7	Needles (obturator + catheter) insertion through the guiding tubes till surface of applicator/ring/ovoids	Catheters and needles smaller than 6F are used (EQ)	I. Used catheters can shift inside the guiding channels; II. Dwell positions are different than intended.	Radiation energy - ionising radiation	R29	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	2	Investigate further risk control	Warning in applicator manual and protocol	3	Provide instructions to use no other than 6F catheter and needles	2	1	Yes
		14.8	Needle insertion channel check															
		14.9	Locking the needles in the guiging tubes by turning the nuts at the distal end of the guiding tubes															
		14.10	Implantation of the tandem	Prespecified tandem is not used, switched to different tandem (EQ)	I. Prespecified applicator tandem does not fit / is not available II. Physician switches to use of different tandem III. Applicator is constructed around 'incorrect' tandem IV. Dwell positions are different than intended	Radiation energy - ionising radiation	R30	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	2	Investigate further risk control	Warning in applicator manual and protocol	3	Provide instructions to not use a different tandem than indicated	2	1	Yes
		14.11	Implantation and assembly of the applicator to the tandem	Applicator is inserted by someone other than the radiotherapist or radiotherapy technologist (UR)	I. The applicator is handled with excessive force; II. The applicator detaches during insertion; III. Parts are able to shift ; IV. Incorrect dwell positions.	Radiation energy - ionising radiation	R31	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	2	Investigate further risk control	Warning in applicator manual and visual inspection	3	Provide instructions to not use excessive force while insering the applicator and who shall insert the applicator	2	1	Yes
				Applicator is not properly assembled to the tandem (PU)	I. Applicator parts are not properly attached to tandem; II. Parts are able to shift; III. Incorrect dwell positions.	Radiation energy - ionising radiation	R32	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	2	Investigate further risk control	Instructions in applicator manual	1 or 3	Provide instructions about how to properly attach the applicator to the tandem and integrate currently used connection mechanism in design of the applicator	2	1	Yes
		14.12	Needles are unlocked by turning the nuts at the distal end of the guiding tubes															
		14.13	Insertion of the needles to correct depth into the patient's tissue using the insertion tool	Needles are inserted with incorrect insertion depth (PU)	I. Needle depth is different than intended; II. Dwell positions are different than intended.	Radiation energy - ionising radiation	R33	Needle tip inserted not on planned depth	Excessive irradiation of healthy tissue or tumour	3	2	Investigate further risk control	Needle insertion depth check and warning in applicator manual	2 and 3	Design interface as such that guiding tube are sorted (bracelet) and provide clear instructions on checking guiding tubes	3	1	Yes

	14.14	Locking the needles in the guiging tubes by turning the nuts at the distal end of the guiding tubes															
	14.15	Removing of the obturators from the catheters	Obturators are not removed from the catheters (PU)	I. Obturators stay in the catheters; II. Obturators are still in the patient while imaging; III. Obturators move while imaging.	Electric energy - magnetic field	R34	Obturators in MRI	Movement of obturators in patient	4	1	Investigate further risk control	Warning in applicator manual and protocol	3	Provide instructions and warning about how to remove the obturators from the needles	4	1	Yes
	14.16	Removing sterilisation cap from the tandem and placing of the gadolinium marker inside of the tandem															
	14.17	Patient is transported to the recovery room															
15. Imaging	15.1	Patient is transported to the MRI room															
	15.2	Insertion depth markings check on the thighs of the patient															
	15.3	Imaging (MRI or CT scan)															
	15.4	Removing the gadolinium markers from the tandem and putting the sterilisation cap on the tandem															
	15.5	Patient is transported to the nursing ward															
16. Treatment planning	16.1	Reconstruction of the applicator and needles	Applicator is incorrectly reconstructed (PU)	I. Applicator not clearly distinguishable on images; II.Treatment plan based on incorrect source path; III. Incorrect dwell positions.	Radiation energy - ionising radiation	R35	Radioactive source is malpositioned	Excessive irradiation of healthy tissue or underdosage of tumour	3	2	Investigate further risk control	Warning in applicator manual and protocol	1 and 3	Design interface such that the applicator is distinguishable on images (line marker channel) and provide clear instructions on how to reconstruct the applicator	3	1	Yes
			Needles are incorrectly reconstructed (PU)	I. Needle length and / or depth is incorrectly reconstructed from images; II. Treatment plan based on incorrect source path; III. Incorrect dwell positions	Radiation energy - ionising radiation	R36	Radioactive source is malpositioned	Slight overirradiation of healthy tissue or underdosage of tumour	2	3	Investigate further risk control	Warning in applicator manual and protocol	3	Provide clear instructions on how to reconstruct the needles, provide a minimal distance between the center of the channels to make sure the needles are distinguishable	2	2	Yes
			Needle channel mix up during reconstruciton (PU)	I. Needle numbers are switched during reconstruction; II. Dwell positions are different than intended;	Radiation energy - ionising radiation	R37	Radioactive source is malpositioned	Slight overirradiation of healthy tissue or underdosage of tumour	3	3	Investigate further risk control	Protocol and training	3	Provide clear instructions on how to number the neeldles, visual check	3	2	Yes
	16.2	Contouring OARs, GTV, HR CTV, and IR CTV															
	16.3	Treatment planning and optimisation															
	16.4	Dose evaluation and verification of plan by radiation oncologist															
	16.5	Verification of treatment plan															
17. Treatment delivery	17.1	Patient is transported to the radiation room															
	17.2	Flexitron HDR transfer tubes are connected to the corresponding channels/needles	Transfer tubes are connected to wrong applicator / needle channel (PU)	I. Dwell times are different than intended.	Radiation energy - ionising radiation	R38	Dwell times of radioactive source are different from planning	Excessive irradiation of healthy tissue or underdosage of tumour	3	2	Investigate further risk control	Transfer tubes check and warning in applicator manual	2 or 3	Design interface as such that guiding tube are sorted (bracelet) and provide clear instructions on checking guiding tubes	3	1	Yes
			Transfer tubes not correctly aligned with applicator (PU)	I. Source fails to progress through transfer tubes; II. Source is stuck.	Radiation energy - ionising radiation	R39	Incorrectly aligned transfer tubes	Excessive irradiation of healthy tissue of tumour	3	1	Insignificant or negligible risk	Visual inspectation and warning in applicator manual	3				
	17.3	Flexitron HDR transfer tubes connection check															
	17.4	Dummy run															
	17.5	Radioactive source is guided through applicator and needles															
	17.6	Flexitron HDR transfer tubes are disconnected from applicator and needles															
18. Applicator removal	18.1	Nut that locks the needles is loosened and all needles are removed from the patient															
	18.2	Applicator disassembly and removed from the patient	Applicator is disassembled and removed by someone other than the radiotherapist or radiotherapy technologist (UR)	I. Applicator is disassembled using excessive force.	Funcitonality - incorrect removal	R40	Incorrect applicator disassembly	Discomfort or painful removal for patient	1	1	Insignificant or negligible risk	Warning in applicator manual and protocol	3				
			Applicator cannot be disassambled (PU)	I. Disassembly of the applicator not possible/difficult; II. User applies excessive force to disassembly the applicator.	Funcitonality - incorrect removal	R41	Incorrect applicator disassembly	Discomfort or painful removal for patient	1	2	Insignificant or negligible risk	None	1				
			Applicator is used for double-fraction (PU)	I. Applicator is not removed because it is used for a double-fraction; II. Applicator is implanted for longer than 24 hours.	Funcitonality - implantation time	R42	Implantation time of applicator longer than 24 hours	Biocompatability issues (Subacute toxicity and implantation effects)	2	4	Investigate further risk control	None	3	Provide instructions to not use the applicator for a double fraction	2	1	Yes
			Applicator is not removed from the patient (PU)	I. Applicator stays implanted in patient.	Funcitonality - incorrect removal	R43	Implantation time of applicator longer than 24 hours	Biocompatability issues (Subacute toxicity and implantation effects)	4	1	Investigate further risk control	Waring in applicator manual	3	Waring in applicator manual, visual check	4	1	Yes
	18.3	Tandem is removed from the patient															
Post-use	**19. Applicator disposal**	19.1	Applicator disposal														

Expected workflow ARCHITECT applicator risk analysis: intended use

5.4: Identification of hazards and hazardous situations								5.5: Risk evaluation				7.1: Risk control option analysis					
Overall process step	**Step Name**	**Step NR**	**What/how description**	**Foreseeable sequence of events**	**Hazard**	**Risk NR**	**Hazardous situation(s)**	**Harm**	**Severity**	**Probability**	**Acceptable?**	**Current process control**	**Risk control option**	**Risk control measure**	**Severity**	**Probability**	**Acceptable?**
First application brachytherapy treatment	**1. Imaging**	1.1	Make MRI scan and reconstruct standard applicator														
		1.2	Upload MRI of the patient from last brachy treatment to RT Pacs														
		1.3	Export MRI from RT Pacs to MIM														
	2. Image segmentation	2.1	Segment target volumes in MIM	I. Target volume of patient is within intended use, but difficult to get plan within constraints II. Patient is irradiated with non-optimal dose distribution / large number of needles is required	Radiation energy - ionising radiation Functionality - sharp interface	R44	Treatment plan non-optimal Many needles required	Slight overirradiation of healthy tissue or underdosage of tumour Painful insertion for the patient Excessive tissue damage	3	3	Investigate further risk control	None	2	Software informs about other plans, asks user to confirm a plan that does not meet all constraints	2	2	Yes
				I. New applicator design based on old applicator II. Tumour regression or inter-fraction variations change patient geometry III. Patient is irradiated with non-optimal dose distribution	Radiation energy - ionising radiation	R45	Treatment plan non-optimal	Excessive irradiation of healthy tissue of tumour	3	4	Investigate further risk control	None	3	Provide instructions that patients with large tumour regression are not selected for patient-tailored applicator	3	3	**No**
		2.2	Segment organs at risk in MIM	I. New applicator design based on old applicator II. Day-to-day or inter-fraction variations change patient geometry III. New applicator cannot be inserted properly / Patient is irradiated with non-optimal dose distribution / Needles are inserted with incorrect depth	Functionality - incorrect measurements Radiation energy - ionising radiation	R46	Failure to implant the applicator Treatment plan non-optimal	Painful insertion for the patient Treatment delay Excessive overirradiation of healthy tissue or underdosage of tumour	3	4	Investigate further risk control	None	3	Provide instructions that patients with large organ movement are not selected for patient-tailored applicator	3	3	**No**
		2.3	Segment vaginal cavity in MIM	I. Vaginal cavity is small / introitus is narrow; II. Difficult to plan source channels; III. Patient is irradiated with non-optimal dose distribution / too few needles	Radiation energy - ionising radiation	R47	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	2	Investigate further risk control	None	2	Software puts constraints on minimum dimensions, asks user to confirm a plan that does not meet all constraints	2	1	Yes
				I. Vaginal cavity has a large volume II. Applicator design has a large volume; III. Excessive force is needed for insertion or applicator cannot be inserted.	Functionality - incorrect measurements	R48	Failure to implant the applicator	Painful insertion for the patient	2	3	Investigate further risk control	None	1	Software slims down applicator after generation of source channels	2	2	Yes
				I. New applicator design based on old applicator II. Day-to-day or inter-fraction variations change patient geometry III. New applicator's position is not fixed without external packing IV. Incorrect position of applicator V. Incorrect dwell positions	Radiation energy - ionising radiation	R49	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	4	Investigate further risk control	None	3	Provide instructions on how to correctly apply packing for the applicator	2	2	Yes
	3. Brachytherapy treatment	3.1	First brachytherapy treatment with currently used applicator														

New applicator design	**4. Applicator modelling**	4.1	Previously used RTStruct and RTPlan are imported in software														
		4.2	Target volume, organs at risk and vaginal cavity structures are converted to meshes (STL files)														
		4.3	Intracavitary applicator structures are extracted and processed														
		4.4	Meshes are pre-processed and smoothened to user preference	I. Smoothing cannot remove all edges / holes in segmentation of vaginal cavity present II. Applicator is printed with sharp edges; III. New applicator cannot be inserted properly / Sharp edges causes discomfort to the patient during insertion	Functionality - sharp interface	R50	Outer surface of applicator contains sharp edges / Failure to implant the applicator	Painful insertion for the patient Treatment delay	2	3	Investigate further risk control	None	2	Software warns about coarseness of outer applicator surface using a metric	2	1	Yes
		4.5	Applicator outer geometry is determined: tandem connection, split plane, entry region														
	5. Trajectory planning/optimisation	5.1	Source channels are planned and optimised	I. Locally curvature constraints are exceeded II. Applicator is printed with channels that are not accessible for source cable / needles III. Needles cannot be inserted IV. Applicator is used without all possible needles	Radiation energy - ionising radiation	R51	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	2	Investigate further risk control	None	2	Software performs additional refined check before final applicator selection and warns about local curvature	2	1	Yes
		5.2	Different optimal configurations are derived based on user-specified parameter	I. Optimal plan lies outside of common range for user-specified parameter II. User chooses plan with non-optimal dose distribution III. Dose distribution still passes constraints IV. Patient is irradiated with non-optimal dose distribution	Radiation energy - ionising radiation	R52	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	3	Investigate further risk control	None	2	Create database of optimal coverage radius parameters; check whether range is valid from time to time	2	2	Yes
		5.3	(More exact) Geometry checks of configurations are performed	I. Invalid channel configuration escapes geometry checks II. Applicator is printed with channels that are not accessible for source cable / needles III. Needles cannot be inserted or IC structure cannot be connected IV. Applicator is used without all possible needles / IC structures	Radiation energy - ionising radiation	R53	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	4	Investigate further risk control	None	2	Software performs additional refined (more exact) check and warns about possible failures	2	2	Yes
		5.4	Dosimetric plans are generated from configurations														
		5.5	Plans are compared by user and one configuration/plan is selected	I. User chooses plan with non-optimal dose distribution II. Dose distribution still passes constraints III. Patient is irradiated with non-optimal dose distribution	Radiation energy - ionising radiation	R54	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	5	Investigate further risk control	None	3	Software informs about other plans, asks user to confirm whether to select an objectively worse plan	2	3	Yes
				I. Difficult to get plan within constraints II. Patient is irradiated with non-optimal dose distribution / large number of needles is required	Radiation energy - ionising radiation	R55	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour	2	3	Investigate further risk control	None	2	Software informs about other plans, asks user to confirm a plan that does not meet all constraints	2	2	Yes
	6. Applicator model generation	6.1	Applicator mesh is post-processed and exported to STL														
		6.2	Final applicator mesh (STL) is sent to Oceanz														

Manufacturing	**7. 3D printing**	7.1	3D printing of the applicator by Oceanz														
	8. Post-processing	8.1	Cleaning of the applicator and source channels by Oceanz														
		8.2	Applicator gets vapor treatment by Oceanz														
	9. Quality assurance check & packing	9.1	Checking if channels are accessible for 6F needles by Oceanz														
		9.2	Packing of applicator by Oceanz														
Transport	**10. Transport**	10.1	Applicator package is sent to Erasmus MC by Oceanz	I. Applicator package is delayed during transport; II. Personalised applicator cannot be used during treatment; III. Another applicator is used; IV. Patient is irradiated with non-optimal dose distribution or treatment delay.	Radiation energy - ionising radiation	R56	Treatment plan non-optimal	Slight overirradiation of healthy tissue or underdosage of tumour Treatment delay	2	5	Investigate further risk control	None	3	Introduce guidelines on when the applicator should be send at the latest	2	5	No
Pre-use	**11. Pre-use checks**	11.1	Unpack applicator package														
		11.2	Integrity check: visually inspect that all parts are delivered intact and undamaged (from transport)														
	12. Cleaning, disinfection and sterilisation of the applicator	12.1	Cleaning of the applicator														
		12.2	Disinfection of the applicator														
		12.3	Sterilisation of the applicator using an autoclave														
		12.4	Assembly check of applicator														
	13. Storage of the applicator	13.1	Wrapping and storing applicator														
Second application brachytherapy treatment	**14. Implantation of the applicator**	14.1	Verification that all correct parts are present														
		14.2	Assembly check of applicator														
		14.3	Handling of applicator														
		14.3	Determination of needle configuration (including depth)	I. Incorrect needle insertion depth is marked; II. Needles are inserted with incorrect depth; III. Incorrect dwell positions.	Radiation energy - ionising radiation	R57	Radioactive source is malpositioned	Excessive irradiation of healthy tissue of tumour Minor organ damage	3	2	Investigate further risk control	Needle insertion depth check and warning in applicator manual	3	Provide clear instructions on how to determine the needle configuration, protocol and warning in applicator manual	3	1	Yes
		14.5	Labelling of the guiding tubes														
		14.6	Connecting the guiding tubes to the applicator channels														
		14.7	Needles (obturator + catheter) insertion through the guiding tubes till surface of applicator/ring/ovoids	I. Faulty applicator design (lumen of needle channels too narrow); II. Too high friction in needle channel; III. User applies excessive force to insert needle; IV. Sharp edge of needle comes in contact with personnel V. Needle buckles/shouts through; VI. Needle penetrates tissue.	Functionality - faulty channel design	R58	Needle tip inserted not on planned depth	Minor organ damage Excessive irradiation of tumour and healthy tissue Cut from sharp surface (personnel)	3	1	Insignificant or negligible risk						
		14.8	Needle insertion channel and depth check														

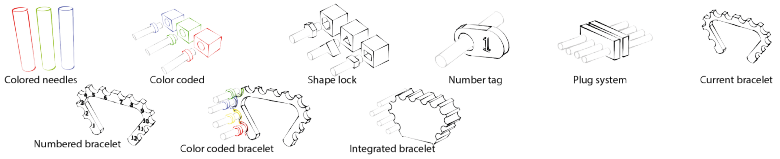
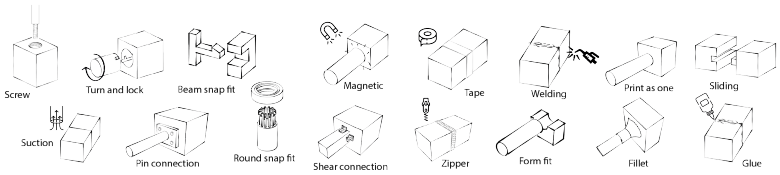
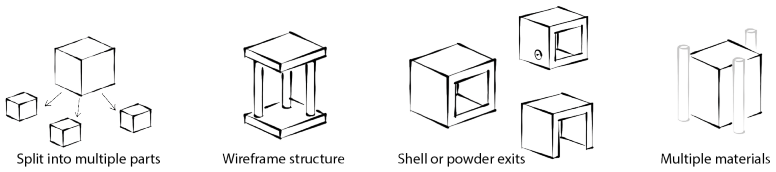
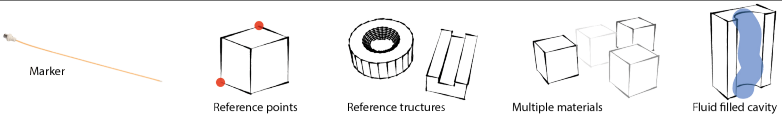
	14.9	Locking the needles by turning the nuts at the distal end of the guiding tubes														
	14.10	Implantation of the tandem														
	14.11	Implantation and assembly of the applicator to the tandem	I. Faulty applicator material; II. Geometric or mechanical properties of the applicator are altered due to change in temperature or humidity.	Functionaliy - faulty material properties	R59	Applicator implantation	Applicator damage	3	1	Insignificant or negligible risk						
	14.12	Needles are unlocked by turning the nuts at the distal end of the guiding tubes														
	14.13	Insertion of the needles to correct depth into the patient's tissue using the insertion tool	I. Needles are inserted with incorrect insertion depth; II. Needles are inserted too deep; III. Incorrect dwell positions.	Radiation energy - ionising radiation	R60	Needle tip inserted not on planned depth	Excessive irradiation of healthy tissue of tumour Minor organ damage	3	2	Investigate further risk control	Operator training, ultrasound guidance/check, warning in applicator manual	1 or 3	Make it able to use the needle insertion tool and provide clear instructions on how to use the needle insertion tool	3	1	Yes
	14.14	Locking the needles by turning the nuts at the distal end of the guiding tubes	I. Needles are not locked properly; II. Needles can move during treatment: III. Incorrect dwell positions.	Radiation energy - ionising radiation	R61	Needle tip inserted not on planned depth	Excessive irradiation of healthy tissue of tumour Minor organ damage	3	2	Investigate further risk control	Operator training, ultrasound guidance/check, warning in applicator manual	1 or 3	Minimize change on displacement of needles when inserted by design and make sure the needles can be locked (nut of guiding tubes or needle lock pins)	3	1	Yes
	14.15	Removing of the obturators from the catheters														
	14.16	Removing sterilisation cap from the tandem and placing of the gadolinium marker inside of the tandem														
	14.17	Patient is transported to the recovery room	I. Patient is transported; II. Applicator is shifted due to movement of the body during transport III. Incorrect position of applicator; IV. Incorrect dwell positions.	Radiation energy - ionising radiation	R62	External motion	Slight overirradiation of healthy tissue or underdosage of tumour	2	2	Investigate further risk control	Warning in applicator manual, packing	3	Provide clear instructions to minimise patient movement	2	2	Yes
15. Imaging	15.1	Patient is transported to the MRI room	I. Patient is transported; II. Applicator is shifted due to movement of the body during transport III. Incorrect position of applicator; IV. Incorrect dwell positions.	Radiation energy - ionising radiation	R62	External motion	Slight overirradiation of healthy tissue or underdosage of tumour	2	2	Investigate further risk control	Warning in applicator manual, packing	3	Provide clear instructions to minimise patient movement	2	2	Yes
	15.2	Insertion depth markings check on the thighs of the patient														
	15.3	Imaging (MRI or CT scan)	I. Applicator disturbs image; II. Reconstruction of the applicator and/or needle channels not possible.	Functionality - visibility	R63	Incorrect applicator material or design	Treatment delay	2	3	Investigate further risk control	None	1	Provide a minimal distance between the center of the channels and perform tests beforehand to ensure the material/applicator is visible on image	1	2	Yes
	15.4	Removing the gadolinium marker from the tandem and putting the sterilisation cap on the tandem														
	15.5	Patient is transported to the nursing ward	I. Patient is transported; II. Applicator is shifted due to movement of the body during transport III. Incorrect position of applicator; IV. Incorrect dwell positions.	Radiation energy - ionising radiation	R62	External motion	Slight overirradiation of healthy tissue or underdosage of tumour	2	2	Investigate further risk control	Warning in applicator manual, packing	3	Provide clear instructions to minimise patient movement	2	2	Yes

16. Treatment planning	16.1	Reconstruction of the applicator and needles															
	16.2	Contouring OARs, GTV, HR CTV, and IR CTV															
	16.3	Treatment planning and optimisation															
	16.4	Dose evaluation and verification of plan by radiation oncologist															
	16.5	Verification of treatment plan															
17. Treatment delivery	17.1	Patient is transported to the radiation room	I. Patient is transported; II. Applicator is shifted due to movement of the body during transport III. Incorrect position of applicator; IV. Incorrect dwell positions.	Radiation energy - ionising radiation	R62	External motion	Slight overirradiation of healthy tissue or underdosage of tumour	2	2	Investigate further risk control	Warning in applicator manual, packing	3	Provide clear instructions to minimise patient movement	2	2	Yes
	17.2	Flexitron HDR transfer tubes are connected to the corresponding channels/needles															
	17.3	Flexitron HDR transfer tubes connection check															
	17.4	Dummy run															
	17.5	Radioactive source is guided through applicator and needles	I. Source is jammed in the channels; II. Soure cannot continue to next dwell position.	Radiation energy - ionising radiation	R64	Radiation treatment	Excessive irradiation of healthy tissue of tumour	4	1	Investigate further risk control	Dummy run and withdrawing of the source when jammed	3	Warning in applicator manual	4	1	Yes
	17.6	Flexitron HDR transfer tubes are disconnected from applicator and needles															
18. Applicator removal	18.1	Nut that locks the needles is loosened and all needles are removed from the patient															
	18.2	Applicator disassembly and removed from the patient															
	18.3	Tandem is removed from the patient															
Post-use	**19. Applicator disposal**	19.1	Applicator disposal														

E

Conceptual designs: how-to's

Table E.1: Chart containing the formulated how-to's and solutions collectd during different brainstorm sessions.

How to prevent needle channel mix-up?	
How to improve guidance of the source through the intracavitary channel(s)?	
How to connect different parts to each other? (reversible and irreversible)	
How to improve printability of the 3D-printed part(s)/ensure that the source channels remain open after printing?	
How to ensure visibility on CT/MRI scans?	

F

Prototyping introduction

To express, visualise and materialise the ideas and concepts, different prototypes have been made. Using these prototypes, it was validated whether a particular solution principle worked. The prototypes made during this project were manufactured using the fused deposition modelling (FDM) printers Anet A8 plus (Anet Technology Co. Ltd, Shenzhen, China) and Ultimaker 3+ (Ultimaker B.V., Geldermalsen, the Netherlands) printers and using Oceanz selective laser sintering (SLS) printers EOS Formiga P1 system (EOS, Krailling, Germany) using polyamide 12 (PA12, EOS PA 2200, Krailling, Germany). The working principles of these different 3D-print techniques are shown in Figure F.1.

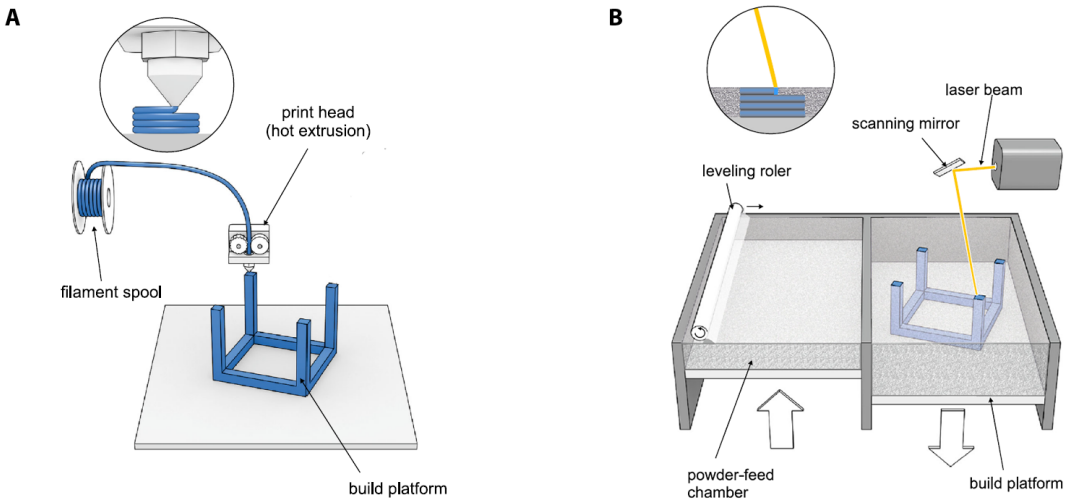


Figure F.1: The two 3D-print technologies that are used to manufacture the prototypes. (a) Fused Deposition Modeling (FMD); (b) Selective Laser Sintering (SLS) [55].

The FMD technique extrudes and selective depositions thermoplastics into layers that build up to create a part whereas SLS uses a high-power laser to sinter small particles of polymer powder into a solid structure. One of the advantages of using the SLS printing technique is that no support structures are needed during printing: powder that is not solidified by the laser supports the next layer.

G

Prototypes design process

G.1. Concept 1

To evaluate if a shell around the wireframe was needed, a wireframe model was developed in Solidworks (SolidWorks, Dassault Systemes, USA) using standard geometric shapes and was printed using the Ultimaker 3+ printer. This prototype can be seen in 5.1.A. From this prototype it became clear that due to the small and long channels, the applicator might not be rigid enough and that it would be possible for tissue to get in between the open space between the channels. To solve both problems, a shell was added around the wireframe. This model was printed using the Anet A8 plus printer and can be seen in Figure G.1. Upon analysing this print, it became clear that the following design aspects needed to be developed further: the notch dimensions for placement of the cervical stopper, the dimensions of the slot for connecting the ovoid guiding tubes, the space needed for the tandem, the IC needle insertion and the thickness of both the shell and the needle guiding tubes.

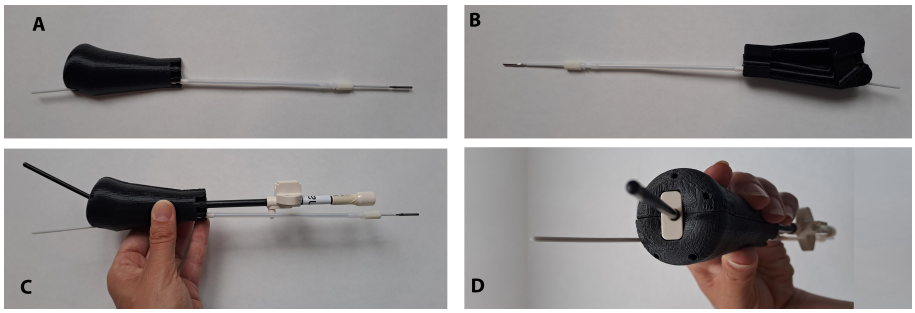


Figure G.1: First 3D-printed model of concept 1: wireframe + shell model.

Figure G.2 shows the prototypes created with the Ultimaker 3+ printer to evaluate different dimensions of both the notch for placement of the cervical stopper and the slot for connecting the ovoid guiding tubes. Using these prototypes, dimensions to ensure a firm fit were determined for both components.

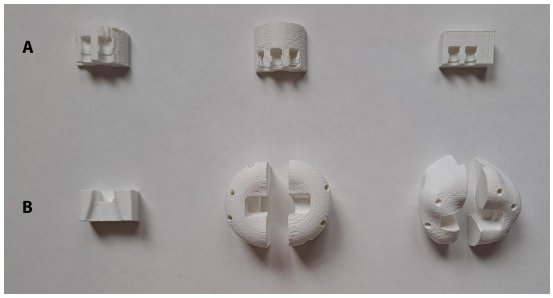


Figure G.2: Prototypes for dimensions of (a) notch for placement of the cervical stopper; (b) slot for connecting ovoid guiding tubes.

When using guiding tubes to lock the needles, it becomes necessary to position the needle channels at a specific offset from the edge of the model's entry region. This requirement imposes limitations on the needle placement options. Therefore, there was investigated if the needles could be locked with needle lock pins in the entry region. This prototype is shown in Figure G.3. However, the dimensions of the needle lock pin slots result in a occupation of space within the entry region, consequently restricting the number of needles that can be placed. Another problem was the dimension of the slot for the needle lock pin, in this prototype these were made using an extruded cut, however the needle lock pin was not firmly fixed. To ensure the proper functioning of the pins, the dimensions of the slots must be examined.

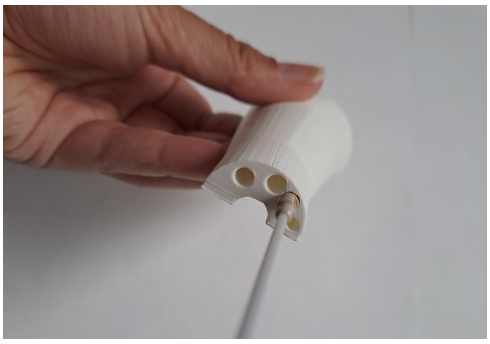


Figure G.3: Problem with space for needles when the needle lock pins are located in the entry region of concept 1.

A needle lock pin contains two protruded ends that, when compressed together, tighten around the needle and locking it in place. Currently, needle lock pins are used in combination with for example the perineal template (see Figure 3.1). The template features holes with partially flat sides, into which the needle lock pins only fit when during insertion the side holes of the pins are oriented in horizontal direction. When the pins are turned 90 degrees (either clockwise or counterclockwise), the flat sides of the holes will push the two protruded ends of the pin together, locking the needle in position. Figure G.4 shows the prototypes which are used to test different dimensions of the holes for ensuring the working principle of the pins.

Figure G.4: Prototypes to test different dimensions for the needle lock pin holes.

Due to the limited number of needles able to be placed when using needle lock pins in the entry region, an alternative was developed: a bracelet connected to the handle in which the needle lock pins are placed. This prototype is shown in Figure G.5 and the geometry of this model is based on the 3D-model of the vaginal cavity of an anonymous patient. Using a bracelet to secure the needle lock pins not only provides space to place more needles in the entry region, but it also provides more space for connecting the handle to the entry region.

The snap-fit connection between the intrauterine tube and the ovoid tubes in this prototype was replicated from the STL. file of the Geneva applicator. The handle's distal end was designed with an outward arch and a thickening section, following the construction of the Geneva ovoid tubes. To ensure correct positioning of the IC ring structure and proper placement of the cervical stopper to the fornices, the top of the model was flattened and given a 6mm radius curve such as a ring applicator has (see Figure G.5.B). Certain issues arose with this design. The bracelet was positioned in line with the entry region at a distance of 35mm, whereby the distance between the bracelet and the connection part of the intrauterine tube led to a problem with the needle lock tool's accessibility to the pins inserted in the bracelet. Another problem was the stiffness of the handle: due to its small diameter (6.5mm) and long length (152mm), it was easy to bend the handle. Furthermore, the IC ring structure proved difficult to clean resulting in remained uncured powder in the channel. Another problem in this prototype was the snap-fit connection with the Geneva intrauterine tube. This connection turned out not to be tight enough as the 3D-printed parts could displace laterally and disconnected easily from the fixation element.

An obturator is used to support the needle during insertion in tissue and to prevent kinking. The needle in the IC structure will not penetrate tissue and therefore an obturator will not be needed during needle placement in the IC channel: only the needle catheter will be placed in the IC structure. A possible problem of this could be that due to the kink in the IC ring channel, the catheter may kink resulting in blocking the source. Therefore, using a flexible implant tube to guide the source through the IC ring channel was considered. This flexible implant tube is more flexible than a needle catheter and contains a button at the end. It was difficult to integrate a locking mechanism for the flexible implant tube and to incorporate the button into the top of the applicator. During a meeting with the medical physicist of the Radiation Oncology department, it was decided to check whether the catheter would kink and block the source when inserted in the IC ring structure. Using a dummy-run cable and the source cable from the afterloader it was validated that the source was able to be guided through the IC ring channel with a 6F catheter inserted.

In order to facilitate the post-processing, cleaning, and sterilization of the IC ring channel, it is necessary for the channel to have an open-ended configuration. Consequently, the end of the IC channel is extended to the surface of the applicator.

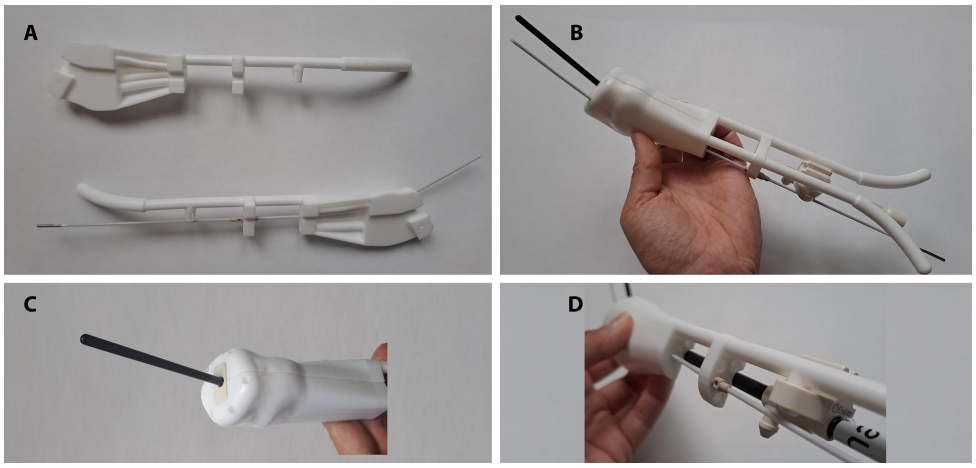


Figure G.5: Concept 1 printed in PA12 with Vapor after treatment; (a) Side view of the 3D-printed parts; (b) Assembled applicator: 3D-printed parts and Geneva intrauterine tube; (c) Rounded top of the personalised applicator; (d) Bracelet distance problem.

Figure G.6 shows the created prototype which was used to evaluate what the optimal dimensions were to ensure a secure snap-fit connection between the 3D-printed parts and the Geneva intrauterine tube. Each snap-fit in the prototype had distinct dimensions. To prevent the 3D-printed parts from being able to displace laterally when connected to the Geneva intrauterine tube, small extrusions were placed at the distal ends of the handles. When the handles are pushed together at the distal end during insertion, these two parts will bump into each other, preventing the 3D-printed parts from rotating outwards.

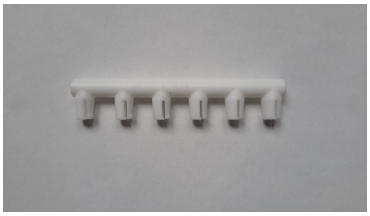


Figure G.6: Prototype of snap-fit connection to Geneva intrauterine tube with different dimensions for the snap-fit.

The centre line of a 22mm Venezia applicator was used for the IC ring structure in the model. The kink in the ring structure made it hard to clean the channel thoroughly resulting in uncured powder being left in the channel. To address this issue, an extra channel was added, extending from the IC ring structure path to the medial site of the 3D-printed parts. This configuration allowed the kinked channel to be cleaned from two sides without occupying significant space that could otherwise be used for needle channels. In

addition, the orientation of this extra channel ensured that when a needle catheter is inserted into the IC ring structure, it cannot unintentionally enter the extra channel.

During a feedback meeting with a radiotherapist from Erasmus MC, concerning the prototype shown in Figure G.5, it was concluded that the distal thickening part of the handle was unnecessary. The radiotherapist indicated that the applicator was not held at these part of the handles, but is held at the tubes close to the connection part of the intrauterine tube and that the thickening part of the handles was used to apply bandage for fixation of the applicator to the thighs of the patient. Therefore, the handles were shortened, while still providing space for bandage. Bandage is used to fixate the applicator to the patient.

Regarding the issue of the accessibility of the needle lock pins in the bracelet, some different design option for the handle were developed. Two of these options can be seen in Figure G.7.

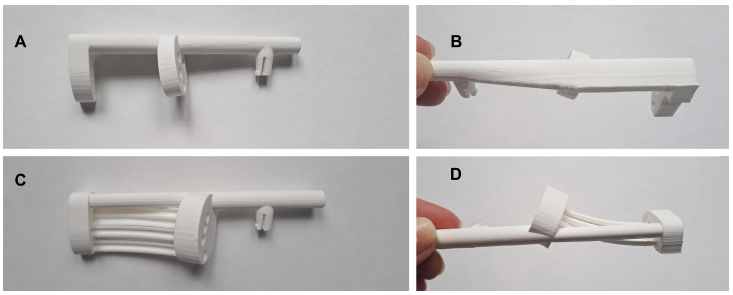


Figure G.7: Two handle options for concept 1; (a) Option 1; (b) Option 2; (c) Close-up option 1; (d) Close-up option 2.

Handle A in Figure G.7 features an extrusion with the width of the entry region, extending till the bracelet aiming to enhance handle stiffness. To ensure the needle lock tool's access to all the inserted pins in the bracelet, the bracelet was rotated outward by 20 degrees. However, this rotation caused misalignment between the pin holes in the bracelet and the corresponding channel holes in the entry region. Consequently, inserting needles from the bracelet into the correct channel in the entry region became more challenging. Therefore, handle B in Figure G.7 was developed. This handle incorporated guiding structures, extending from the needle lock holes in the bracelet to the corresponding channels in the entry region. In this way, the needle will be guided to the correct channel in the entry region and needle channel mix-up will be prevented. The guiding structure consists of half tubes, swept with a 80mm radius from the entry region to the bracelet. The bracelet is positioned 35mm from the entry region. Using this handle design, a new prototype was made, shown in Figure G.8. The diameter of the handle in this prototype was 7.5mm and the thickness of the guiding structures was 1mm.

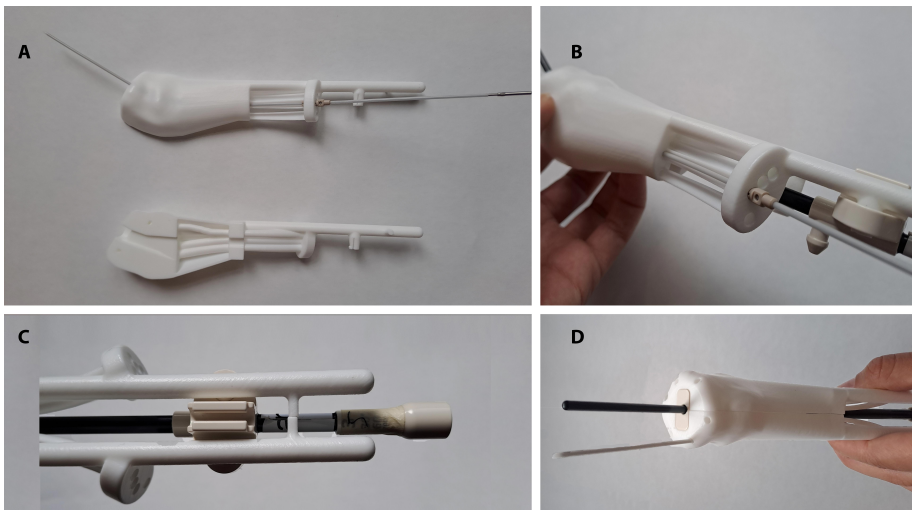


Figure G.8: Concept 1 printed in PA12 with Vapor after treatment; (a) Side view of the 3D-printed parts; (b) Close-up of bracelet and needle guiding structure; (c) Close-up of the extrusion parts to prevent lateral rotation; (d) Close-up of the cervical stopper placement.

The two small extrusion that were added at the distal end of the handles to prevent the 3D-prints from from rotating outwards (see Figure G.8.C.) limited the available bandage space. Hence, another solution to prevent the 3D-prints from rotating outward was developed. The Geneva ovoids feature a small extrusion part at the connection with the intrauterine tube, see Figure G.9.A. When the Geneva applicator is spread laterally, this extrusion part limits the lateral displacement of the ovoids and prevents the ovoids from disconnecting from the cervical stopper. To limit the lateral displacement of the 3D-printed parts, such extrusions were added to the model, as is shown in Figure G.9.B.

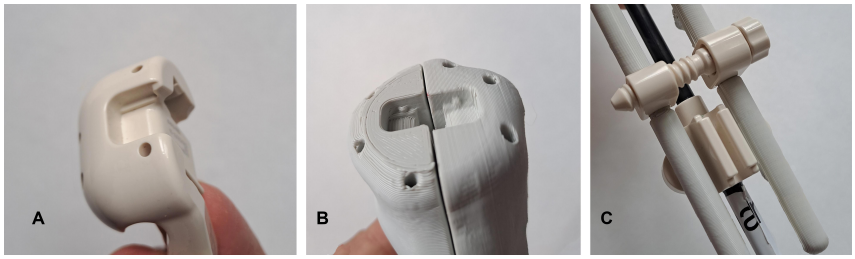


Figure G.9: Close-up of: (a) connection Geneva ovoids with cervical stopper; (b) connection 3D-prints with cervical stopper; (c) narrowed part of the handles (diameter 6mm) for placement of the spreading clip for fixation of the 3D-printed parts.

During another feedback session with a radiotherapist and a medical physicist it was concluded that the use of the spreading clip to fixate the 3D-printed parts was desired. Therefore, the handles were narrowed proximal of the intrauterine tube connection part to a diameter of 6mm. The spreading clip could then be attached to these narrowed handles to firmly fixate the 3D-printed parts in medial position, see Figure G.9.C.

G.2. Concept 2

Using standard geometric shapes, concept 2 was modeled in Solidworks (SolidWorks, Dassault Systemes, USA) and printed using the Anet A8 plus and the Ultimaker 3+ printers. Using these prototypes, the length of the extrusion for the click mechanism was determined. From the STL. file of the Geneva applicator, the proximal end of the ovoid tube was printed. The printed ovoid tube did not fit in these first prototypes, as can be seen in Figure G.10.A. From a 3D-model of a vaginal cavity of an anonymous patient, a personalised model was made in which the insertion space of the ovoid tube and the clicking mechanism were adjusted. The 3D-model of the vaginal cavity was cut and the bottom of the cut was extruded 20mm. This extruded part is used to create the click mechanism for the ovoid tubes and providing the slots for connecting the guiding tubes. This prototype is shown in Figure G.10B and C. The ovoid tube could be inserted from the lateral side of the model and clicked in the model by moving the tubes inward, as can be seen in Figure G.10B and C.

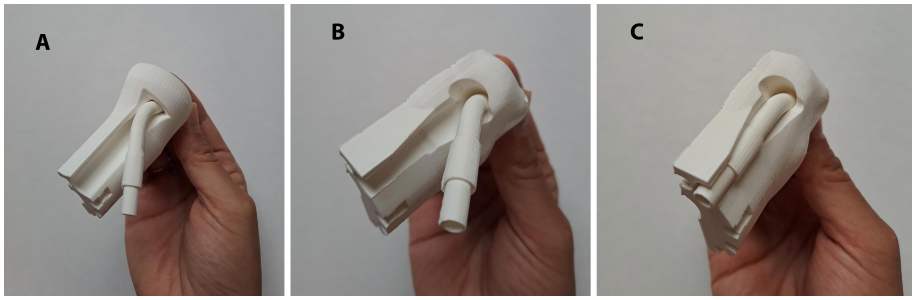


Figure G.10: Concept 2 models; (a) Model in which the space to insert the ovoid tube is too small, it can not be fully inserted in the model; (b) Model in which the space to insert the ovoid tube is sufficient: it ca be fully inserted in the model; (c) The ovoid tube can be turned and clicked in the model.

After it was validated that the click systems for both the ovoid tubes and the guiding tubes worked, this model was printed in PA12. This prototype can be seen in Figure G.11.

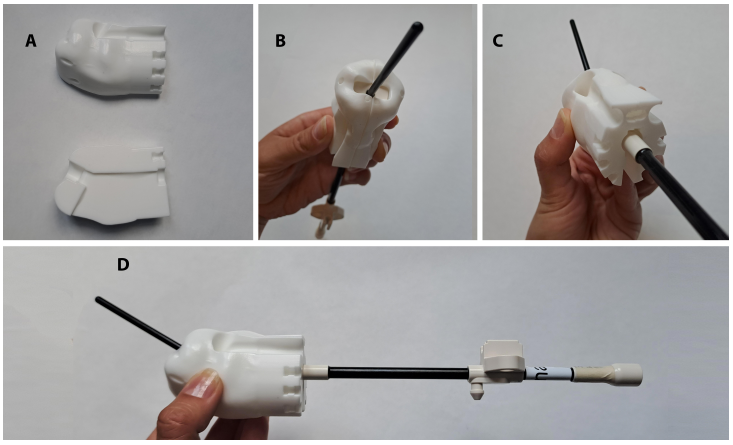


Figure G.11: Concept 2 printed in PA12; (a) Side views; (b) Close-up of the cervical stopper placement; (c) Close-up of the click system and the entry region; (d) Side view of assembled applicator: 3D-printed parts and Geneva intrauterine tube.

This prototype featured enough space for the placement of the Geneva intrauterine tube. As is shown in Figure G.11.B, the cervical stopper was not aligned with the surface of the 3D-printed parts. This is necessary to ensure proper positioning of the IC structure and proper placement of the cervical stopper to the fornices. Therefore, just as is done in concept 1, the top of the model was flattened and given a 6mm radius curve. This model was printed and can be seen in Figure G.12.

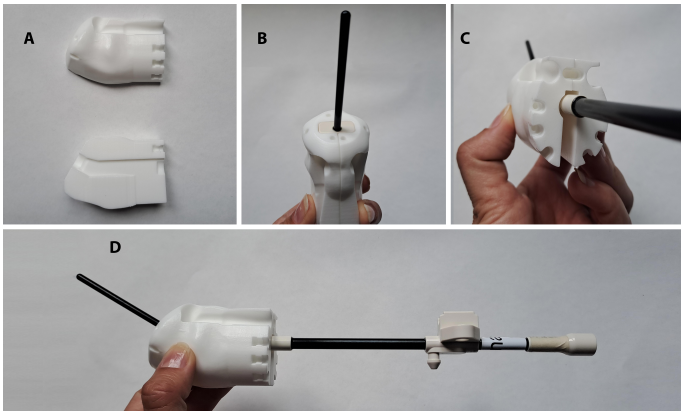


Figure G.12: Concept 2 with rounded top, printed in PA12; (a) Side views; (b) Close-up of the cervical stopper placement; (c) Close-up of the click system and the entry region; (d) Side view of assembled applicator: 3D-printed parts and Geneva intrauterine tube.

As can be seen in Figure G.12.D, the extrusion part is relatively straight. This is not conform the geometry of the vaginal cavity: the vaginal cavity usually tapers from the fornices to the introitus. To correct this, the extruded part of the model is tapered with an angle based on the 3D-model of the vaginal cavity, see Figure G.13.B.

Figure G.13: Difference in tapered extrusion; (a) first design; (b) 3D-model of vaginal cavity; (c) tapered extrusion based on 3D-model of vaginal cavity.

As with concept 1, there must be prevented that the 3D-printed parts can displace laterally when assembled to the Geneva intrauterine tube. Therefore, also in concept 2 the extrusion parts in the notches are added to prevent lateral displacement.

Experiment dose attenuation properties of PA12

H.1. Protocol experiment

Materials

- Test box 1: two Oceanz PA12 L-shaped 3D printed parts with closed surface (Fig. H.1.a) which have had the vapor post-treatment;
- Test box 2: two Oceanz PA12 L-shaped 3D printed parts with open surface (Fig. H.1.b);
- At least one flexible implant tube 6F, SL, 50cm (Nucletron B.V., Veenendaal, the Netherlands);
- Cutting tool for the flexible implant tube;
- Tape;
- Hand guillotine paper cutting machine (or other paper cutting tool);
- Seven radiochromic film segments: Gafchromic film type EBT3 (Ashland Advanced Materials, Bridgewater, United Kingdom) (dynamic dose range 0.2 cGy – 10 Gy). Dimensions of the GafChromic film segments: 4cm x 6.5cm;
- Flexitron afterloader;
- Water tank;
- One transfer tube;
- Flatbed scanner;
- Marker (preferably waterproof).

Methods

The two test boxes used in the article of Cunha et al. were recreated using SolidWorks 2022 [49]. The test boxes consist each of two L-shaped parts. The first box had a closed surface and was used to measure the dose attenuation properties of Oceanz PA12 (H.1.a). The second box had an open surface and was used to make the comparison with the dose attenuation properties of water (Fig. H.1.b). Both boxes were printed in PA12 by Oceanz using SLS. After printing and cooling, box 1 received a vapor treatment to make the material more waterproof.

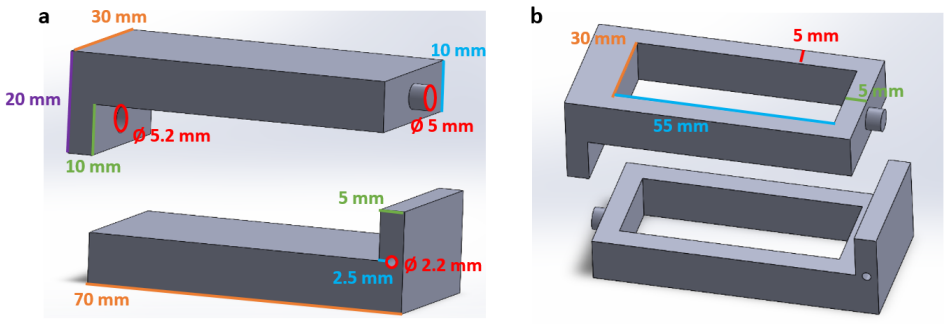


Figure H.1: The two 3D printed test boxes; (a) the two L-shaped parts which are printed in PA12 using SLS and which had the vapor post-treatment; (b) the two L-shaped parts with open surface which will be printed in PA12 using SLS.

From a sheet of Gafchromic EBT3 (approximately 20cm x 25cm) seven pieces of smaller segments were cut using a hand guillotine paper cutting machine. Due to the cutting, separation of the layers of the Gafchromic EBT3 film sheet may occur (delamination). Therefore, an extra 5mm marge was included at each side to be cut. The dimension of the seven smaller pieces were 4cm x 6.5cm. They were cut in a way that one of the 4cm sides of the segments did not need to be cut (edge of the larger sheet).

When holding the film segments in landscape orientation, with the uncut 4 cm side to the right, on six of the seven film segments a number (1 to 6) was written with the marker. In addition, an arrow was written in the corner, pointing to the outside of the segment. The arrow ensured consistent orientation when the film segments were placed in the test boxes, see Fig. H.2. The segment without a number was the test segment and was to validate if the test setup worked. The segments numbered 1-3 were be placed in test box 1 (closed surface), segments 4-6 were be placed in test box 2 (open surface).

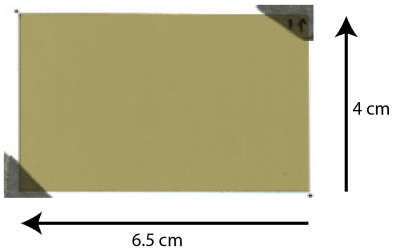


Figure H.2: Gafchromic film segment 1

.

The test segment was placed inside test box 1 (between the two L-shaped 3D-printed parts). The uncut 4 cm side of the film segment was placed besides the needle channel. The arrow pointed to the outside. The flexible implant tube was cut to length and was placed inside the 4cm long channel in the 3D-printed part. Inside the channel were 7 dwell positions spaced 5 mm apart. A dose plan with an 192Ir source and using the TG-43 dose calculation formalism was designed with equal dwell time at each of the 7 dwell positions, see Fig. H.3. The time was normalised to deliver 1500 cGy at 1 cm radially from the centre dwell position. This resulted in a dwell time of 38.2 seconds per dwell position. Therefore, the total channel time and thus the total irradiation time per box was 267.4 seconds.

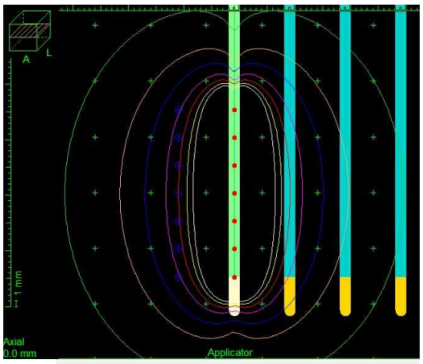


Figure H.3: Irradiation plan. The red dots are the activated well positions, spaced 5mm apart. The red line represents 1500cGy isodose line.

The button at the end of the flexible implant tube was taped to the test box to prevent it from moving during the irradiation. To prevent the effect of radiation scattering by the floor on the film segment, the test box was taped to a plastic PET bottle filled with water which was placed in the middle of a water tank. The flexible implant tube was connected to the transfer tube, see Fig. H.4. This connection must always be outside the water tank to avoid damage to the source and/or afterloader.

The dose plan was delivered using channel 1 of the Flexitron afterloader. After the irradiation was done, the transfer tube was uncoupled form the flexible implant tube and the flexible implant tube was removed from the test box. The test segment was removed from the test box and inspected for colour change. When exposed to radiation, the yellow film segment undergoes a change in optical density, which is

Figure H.4: Experimental set up. Side view of the Flexitron afterloader (left), water tank and plastic bottle with test box 1 taped to it. The flexible implant tube is inserted in the test box and connected to the afterloader.

proportional to the amount of radiation absorbed. The more radiation absorbed, the darker/bluer the film segment will be. There was a clear colour change visible in the test film segment, which indicated that the test setup worked.

Film segment number 1 was placed in test box 1 (closed surface) and irradiated with the same plan as was used for the test segment. Afterwards, film segment number 4 was placed in test box 2 (open surface) and irradiated. For each irradiation the test boxes were altered, to minimize the effect of radioactive source decay. After all of the six film segments were irradiated, they were allowed to self-develop for 24 hours.

H.2. Individual results of experiment

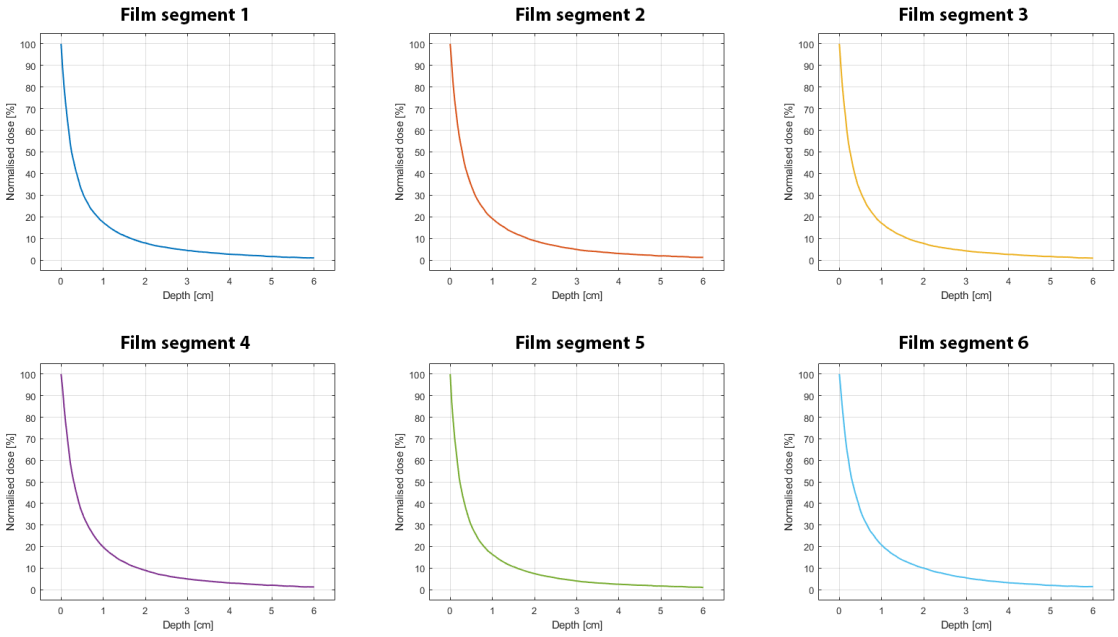


Figure H.5: Percent dose depth curve per film segment.

H.3. Pictures of set-up and material

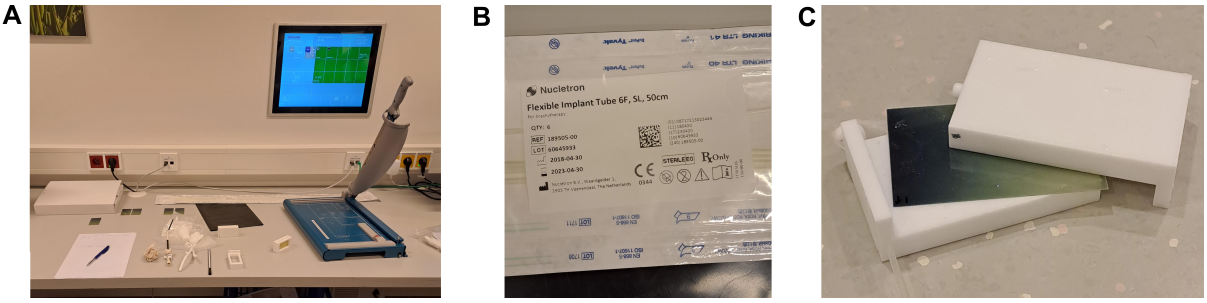


Figure H.6: Pictures taken during the experiment; (a) work space; (b) close-up of the label of the flexible implant tube that was used; (c) close-up of test box 1 with the flexible implant tube inserted and an irradiated Gafchromic EBT3 film segment.

H.4. Matlab code experiment

```
%% Matlab code from scanned film segment to dose
clear all
close all
clc

%% Load calibration data (from Excel Peter)
%calibration = xlsread('Kalibratie_bestand.xlsx');

%% Load scanned film image
%PA12 films (test box 1)
film_image{1} = imread('film_300_001_cropped_72dpi.tif');
film_image{2} = imread('film_300_002_cropped_72dpi.tif');
film_image{3} = imread('film_300_003_cropped_72dpi.tif');
%Water films (test box 2)
film_image{4} = imread('film_300_004_cropped_72dpi.tif');
film_image{5} = imread('film_300_005_cropped_72dpi.tif');
film_image{6} = imread('film_300_006_cropped_72dpi.tif');

%% Extract color channel data from the film image
for i = 1:6
film_R{i} = double(film_image{i}(:,:,1));
film_G{i} = double(film_image{i}(:,:,2));
film_B{i} = double(film_image{i}(:,:,3));

% Calculate optical density from GreyValue
OD_R{i} = log10((2^16) ./ film_R{i});     %Optical Density R channel
OD_G{i} = log10((2^16) ./ film_G{i});     %Optical Density G channel
OD_B{i} = log10((2^16) ./ film_B{i});     %Optical Density B channel

% Fitparameters per kleurkanaal
fit_par_R = [2532.3523 0.062625 4021.4854];  % Fitparameters R channel (
    mail Peter)
fit_par_G = [3447.46 0.0029012 5809.5425];   % Fitparameters G channel (
    mail Peter)
fit_par_B = [5470.2997 0.063173 14271.19];   % Fitparameters B channel (
    mail Peter)

% Calculate dose per channel
Dose_R{i} = -(fit_par_R(1) - fit_par_R(3) * 10.^-OD_R{i}) ./ (fit_par_R(2)
    - 10.^-OD_R{i});
Dose_G{i} = -(fit_par_G(1) - fit_par_G(3) * 10.^-OD_G{i}) ./ (fit_par_G(2)
```

```
    - 10.^-OD_G{i});
Dose_B{i} = -(fit_par_B(1) - fit_par_B(3) * 10.^-OD_B{i}) ./ (fit_par_B(2)
    - 10.^-OD_B{i});

% Average the dose of the 3 channels
Dose{i} = (Dose_R{i} + Dose_G{i} + Dose_B{i}) ./ 3000; % Divide by 3 to get
     average dose of three channels, divide by 1000 to go from mGy to Gy
Dose{i}(:, end) = []; %remove last column (net niet allemaal even netjes
    recht gelegd in Photoshop)

Dose{i} = fliplr(Dose{i}); %Flip dose matrix
%Dose{i}(:, 1:28) = []; %Remove columns depth 0-1cm because of
    oversaturation (Cunha et al.)

mean_Dose{i} = mean(Dose{i}); %Mean dose

% Convert pixels to depth in mm
depth = linspace(0, 6, length(mean_Dose{i}));  % Pixel size in mm: 72 dpi
    -> 1 px = 0.352778 mm

% Plot dose profile
figure()
imagesc(Dose{i})
xlabel('Length [pixels]')
ylabel('Width [pixels]')
title(sprintf('Film segment %d',i))
colorbar;
caxis([0 57]);
title(colorbar,'Dose [Gy]')
axis equal

% Pot mean dose of average of the 3 channels of the film segments
figure(7)
hold on
plot(depth, mean(Dose{i}),'LineWidth',1.5)
hold off
end
grid on
legend('Film 1 (PA12)', 'Film 2 (PA12)', 'Film 3 (PA12)', 'Film 4 (water)',
     'Film 5 (water)', 'Film 6 (water)')
legend('Location','eastoutside')
ylabel('Dose [Gy]')
xlabel('Depth [cm]')
title('Dose all film segments')
xlim([-0.5 6.5])

%% Calculate Percent depth dose (PDD curve)
for i = 1:6
max_dose(i) = max(mean_Dose{i});        % Max dose per film [Gy]

for j = 1:length(mean_Dose{i})
    pdd{i}(j) = mean_Dose{i}(j) /  max_dose(i) * 100; % Dose percent of max
         dose per film [%]
end

% Plot dose depth curve
figure(8)
hold on
```

```
plot(depth, pdd{i}, 'LineWidth',1.5);
xlim([-0.5 6.5])
ylim([-5 105])
hold off
grid on
end
legend('Film 1 (PA12)', 'Film 2 (PA12)', 'Film 3 (PA12)', 'Film 4 (water)',
    'Film 5 (water)', 'Film 6 (water)')
legend('Location','eastoutside')
xlabel('Depth [cm]');
ylabel('Normalised dose [%]');
title('Percent dose depth curve per film segment')

%% Mean of 3 PA12 film segments and 3 water film segments
mean_PA12 = (mean_Dose{1} + mean_Dose{2} + mean_Dose{3}) ./ 3;
mean_water = (mean_Dose{4} + mean_Dose{5} + mean_Dose{6}) ./ 3;

max_dose_PA12 = max(mean_PA12);
pdd_PA12 = (mean_PA12 ./ max_dose_PA12) .* 100;

max_dose_water = max(mean_water);
pdd_water = (mean_water ./ max_dose_water) .* 100;

% Plot
figure(9)
hold on
plot(depth, pdd_PA12, 'LineWidth',1.5);
plot(depth, pdd_water, 'LineWidth',1.5);
xlim([-0.5 6.5])
ylim([-5 105])
hold off
grid on
legend('PA12', 'water')
legend('Location','eastoutside')
xlabel('Depth [cm]');
ylabel('Normalised dose [%]');
title('Average percent dose depth curve water versus PA12')

%% Plotting all mean PA12 and water data points with average curve
figure(10)
hold on
plot(depth, mean_Dose{1}, '.', 'LineWidth', 0.5, 'Color', [0 0.4470
    0.7410]);
plot(depth, mean_Dose{2}, '.','LineWidth', 0.5, 'Color', [0 0.4470 0.7410])
    ;
plot(depth, mean_Dose{3}, '.','LineWidth', 0.5, 'Color', [0 0.4470 0.7410])
    ;
plot(depth, mean_PA12, 'LineWidth', 1, 'Color', [0 0.4470 0.7410]);
plot(depth, mean_Dose{4}, '.','LineWidth', 0.5, 'Color', [0.8500 0.3250
    0.0980]);
plot(depth, mean_Dose{5}, '.','LineWidth', 0.5, 'Color', [0.8500 0.3250
    0.0980]);
plot(depth, mean_Dose{6}, '.','LineWidth', 0.5, 'Color', [0.8500 0.3250
    0.0980]);
plot(depth, mean_water, 'LineWidth', 1, 'Color', [0.8500 0.3250 0.0980]);
xlabel('Depth [cm]');
ylabel('Dose [Gy]');
xlim([-0.5 6])
```

```
grid on
title('Average dose of film segments');
hold off

%Plotting only the average curve
figure(11)
hold on
plot(depth, mean_PA12, 'LineWidth', 1.5, 'Color', [0 0.4470 0.7410]);
plot(depth, mean_water, 'LineWidth', 1.5, 'Color', [0.8500 0.3250 0.0980]);
xlabel('Depth [cm]'); ylabel('Dose [Gy]');
legend('PA12', 'water');
xlim([-0.5 6])
grid on
legend('PA12', 'water')
legend('Location','eastoutside')
title('Average dose PA12 and water');
hold off
```

Reasoning Harris profile scores

Table I.1: Completed Harris profiles of the two concept designs.

Criteria	Concept 1 -2	Concept 1 -1	Concept 1 +1	Concept 1 +2	Concept 2 -2	Concept 2 -1	Concept 2 +1	Concept 2 +2
1. Possible IS needle planning options				■		■		
2. Needle insertion			■					■
3. Needle locking system			■					■
4. Printability/cleanability of the needle channels			■					■
5. Reconstruction of applicator on MRI			■					■
6. Component to reduce channel mix-up				■		■		

Concept 1 scores higher on the first criterion. This is due to the fact that the needle planning options evaluation done in Section 6.2 suggests that Concept 1 provides more space for potential needle placement in the top of the applicator compared to Concept 2. This is due to the space required for the ovoid tubes in Concept 2. In addition, during the applicator generation in Solidworks in the workflow validation process (Section 6.3), it was not possible to implement the chosen needle configuration in Concept 2 due to the space required for the ovoid tubes. This suggests that in Concept 2, not all optimal needle configuration may be achievable. Therefore, Concept 2 scores lower on this criterion.

Concept 2 scores higher on the second criterion. This is because the needle locking system used in Concept 2 (guiding tubes) is already employed in the currently used applicators, ensuring its functionality. In Concept 1, needle lock pins are used for needle locking. This is also a currently used system in the perineal templates of the Venezia applicator. However, this locking system is not standard in every procedure, and thus might cause some difficulties for the user.

For the third criterion, Concept 2 scores higher. The workflow validation process has confirmed that all IS needle channels in both Concept 1 and Concept 2 can be cleaned to ensure accessibility for 6F needles However, one of the two IC ring channels in Concept 1 could not be properly cleaned (uncured powder remained in the channel) and therefore was not accessible for the 6F needle catheter.

Concept 2 scores higher on the fourth criterion. MRI markers can be placed in both the Geneva tandem and the Geneva ovoid tubes, as is also currently done in a Geneva applicator. In Concept 1, the MRI marker can only be placed in the Geneva tandem. In addition, due to the longer and curved needle channels in this concept, it might be more challenging to reconstruct the needles. However, this was discussed with a radiotherapy technologist who indicated that it should still be feasible to reconstruct Concept 1.

On the final criterion, Concept 1 scores higher. Due to the extending entry region of Concept 1 beyond the introitus, it is possible to validate from outside the patient which channel a needle is being inserted into. Moreover, the needle will be guided from the bracelet to the correct needle channel in the entry region. In Concept 2, it is not possible to discern from outside the patient which needle is placed in which channel. A 3D-printed personalised bracelet can be printed and clicked on the ovoid tubes to separate the guiding tubes, similar to the working principle of the current bracelet. However, Concept 2 does not include an additional component to prevent needle channel mix-up.

J

Protocol user experience experiment

Figure J.1: F.l.t.r: Geneva applicator, concept 1 personalised applicator and concept 2 personalised applicator will be inserted in the phantom by experienced users.

Description
Participants are asked to assemble and insert the two 3D-printed customized applicators and the in the clinic currently used Geneva applicator in a phantom and to insert a needle in one of the needle channels. Afterwards, the participants are asked to fill in a questionnaire about the user-friendliness of the designs and working principles of the two prototypes and the Geneva applicator.

Purpose
The purpose of this research study is to identify design improvement points by evaluating how the user handles three different applicators during assembly and insertion in a phantom.

Participants
The experiment will include 3 participants working in the field of radiotherapy in the Erasmus MC. The participants are adults and have experience with the assembly and/or implantation of applicators for brachytherapy for cervical cancer.

Location
The experiment will place at Erasmus MC. The room in which the experiment will take place must include a table on which the phantom can be placed.

Materials
Applicators

- Geneva tandem: angle 30 degrees, length 80mm. The tandem will be already inserted in phantom;
- Geneva 25mm ovoid pair;
- Geneva ovoid tubes;
- Ovoid guiding tubes corresponding to size of the Geneva applicator;
- Vaginal cap guiding tubes for locking the needle in concept 2;
- Concept 1 3D-printed applicator based on anatomy of phantom;

- Concept 2 3D-printed applicator based on anatomy of phantom;

Applicator accessories

- 2 ProGuide 6F needles;
- 2 obturators;
- 5 needle lock pins;
- Needle lock tool;
- Vaginal packing;
- Speculum;
- Medical tweezer (for inserting vaginal packing if needed);

Other

- Phantom;
- Questionnaire for participants;
- Notebook + pencil or laptop to take notes;

Methods
The participants will have a sheet with assembly instructions of three different applicator types (Geneva applicator and a 3D-printed prototype of concept 1 and 2). The participant will place one ProGuide 6F needle in a predesigned needle channel till the surface of one of the applicator types, lock the needle in place and thereafter the participants will assemble and insert the applicator in a phantom. To stabilize the applicator inside the phantom, the participants may use as much vaginal packing as they think is necessary. The researcher will time the procedure execution time and will take notes on how the participant is handling the applicators. The procedure time will be stopped when the participant says that he or she is finished with the procedure. The participants will be asked to fill in a questionnaire about the design and the feasibility of the applicator type. This procedure will be repeated using the other two applicator types. There will be only 1 experimental group (no control group). The experiment will take approximately 45 minutes to complete. .

To evaluate the designs of the two 3D-printed prototypes and to identify design improvement points, the questionnaire will consist of three parts. The first part will be the System Usability Scale questionnaire, the second part will be a questionnaire containing general questions about the designs and the third part will be a Harris Profile.

Data interpretation
The data that will be collected is the name and profession of the participants and their answers to the questionnaire (which will be printed by the researcher and filled in with pen by the participants). For additional information about the data management, see the data management plan.

Applicator #1 assembly instructions

1. Take the left applicator part and insert the needle lock pin in the marked hole (see Figure 1); **The pin only fits when the side holes of the pin are oriented in horizontal direction, as is shown in Figure 1;**

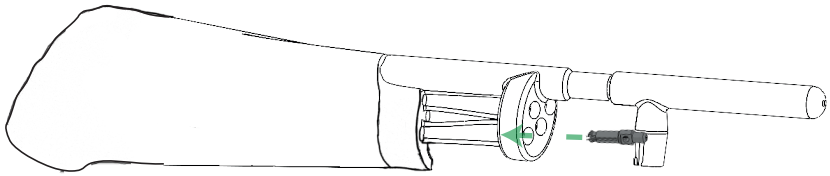


Figure 1

2. Put the ProGuide 6F needle (catheter+obturator) through the lock insert and insert the tip of the needle up to the surface of the applicator as is shown in Figure 2;

Figure 2

3. Move the needle lock tool over the protuding end of the lock pin and turn the pin 90 degrees (either clockwise or counter clockwise) as is shown in Figure 3a;

a *b*

Figure 3

4. After te needle is locked, one of the side holes must face upwards as is shown in Figure 3b;

5. Insert the left applicator part in the phantom and assemble it to the already inserted Geneva tandem. Thereafter, insert and assemble the right applicator part to the tandem.

Applicator #2 assembly instructions

1. Insert the required Ovoid Tube into the applicator parts by slightly rotating the applicator part. Note that the Ovoid Tube marked number 1 should be inserted in the left applicator part and the Ovoid Tube marked number 2 should be inserted in the right applicator part, as can be seen in Figure 1;

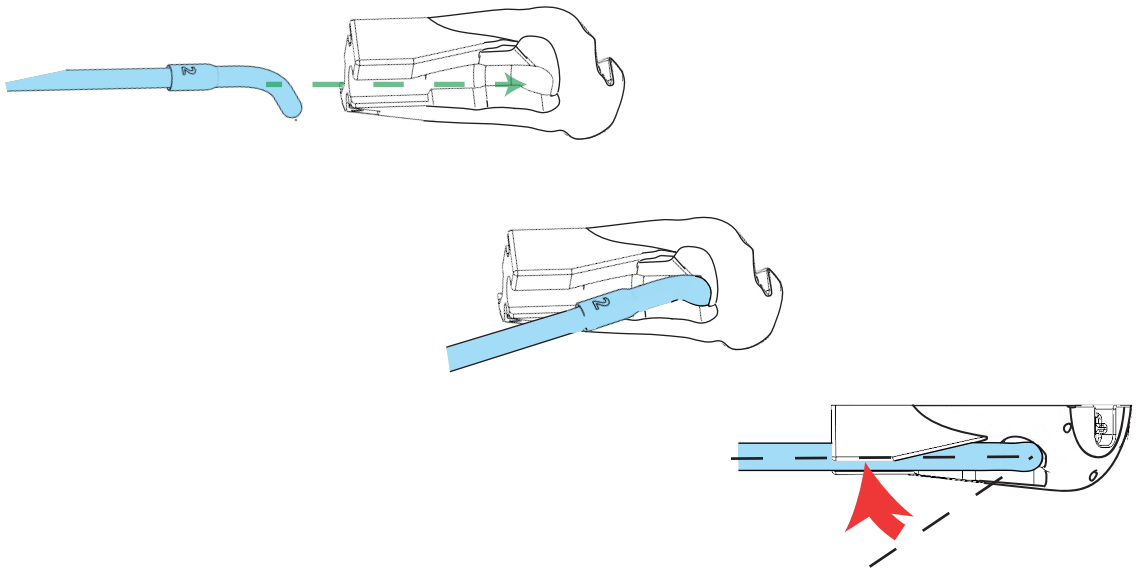


Figure 1

2. Take the obturator and insert it into the ProGuide needle. Insert the ProGuide needle into the Guiding tube. Fit the GuidingTube into the preferred slot of one of the two applicator parts, see Figure 2;

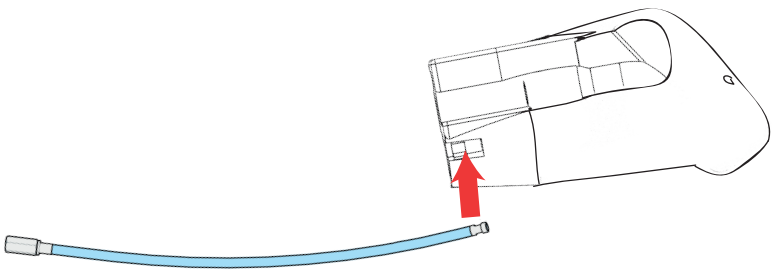


Figure 2

3. Insert the tip of the needle up to the surface of the applicator part. Lock the ProGuide needle by tightening the nut.

4. Insert one part of the applicator in the phantom and assemble it to the already inserted Geneva tandem. Thereafter, insert and assemble the other applicator part to the tandem.

K

User experience experiment: feedback radiotherapist-oncologists

K.1. Radiotherapist-oncologist 1

Due to circumstances, the first radiotherapist-oncologist was unable to complete the questionnaire. Nevertheless, following feedback on the designs of the two prototypes was received during the experiment:

Prototype Concept 1

- The entry region of this prototype extends to outside the patients' introitus and will slightly stretch the muscle. Therefore, the muscle will be under constant tension when the applicator is inserted, which is not comfortable for the patient;
- The width of the applicator does not cause problems during insertion and assembly;
- Adding vaginal packing to stabilise the applicator inside the vaginal cavity seems not needed: due to the shell there is no space for it and the applicator was positioned firmly enough without vaginal packing;
- This prototype does not tend to move laterally after insertion and assembly to the Geneva tandem. Therefore, fixation of the parts using the spreading clip is not necessary;
- Due to the fact that the two handles in this prototype are positioned higher than the ovoid tubes are in the Geneva applicator, it is not possible to slide the fixation clip on the fixation element. However, the use of the fixation clip is desirable;
- The friction in the needle channels of the applicator parts makes needle insertion difficult. In addition, when the needle lock pin is already placed in the bracelet it will probably take a lot of force to insert the needle into the tissue. This should be able to go really smooth and quickly using the needle insertion tool.

Prototype Concept 2

- The click-system of the left applicator part does not work as well as the click-system of the right part. Both sides must be really secure, otherwise the 3D-print is likely to disconnect from the ovoid tube in the vaginal cavity during insertion (due to the used force);
- This prototype does tend to move laterally after insertion and assembly to the Geneva tandem. Therefore, it would be necessary to fixate the ovoid tubes using the spreading clip;
- Adding vaginal packing to stabilise the applicator inside the vaginal cavity seems not needed;
- Due to the fact that ovoid guiding tubes are used, it is easy to lock the needles.

Other comments

- Before insertion, the radiotherapist-oncologist wet the applicators with water so they would be easier to insert;
- The radiotherapist-oncologist does not currently use the spreading clip in the clinic because it is uncomfortably positioned against the patient's legs;
- No problems occurred during insertion of both concepts in the phantom: they were both not too big or too wide and were nice to grip. However, the radiotherapist-oncologist found prototype 2 a little harder to insert and assemble compared to prototype 1;
- If the patient does not have vaginal involvement, the radiotherapist-oncologist would use Concept 2, because in her opinion this concept is easier and faster to insert and assemble;
- Based on patient comfort, the radiotherapist-oncologist would use Concept 2 because this concept does not extend to outside the introitus of the patient. However, based on position (connection of the cervical stopper and the 3D-printed parts and tendency to displace laterally) she would use prototype 1.

K.2. Radiotherapist-oncologist 2

Questionnaire

A. Design questions

5 questions about the design of the prototypes which will be answered using a 1-5 scale (1: strongly disagree, 5: strongly agree). The left table can be used to answer the questions for prototype 1, the right table for answering the questions for prototype 2. For example:

Strongly disagree				Strongly agree
	x			
1	2	3	4	5

Strongly disagree				Strongly agree
			x	
1	2	3	4	5

1. It was easy to insert and lock the IS needle;

	x			
1	2	3	4	5

				x
1	2	3	4	5

2. It was easy to connect the 3D-print to the cervical stopper;

				x
1	2	3	4	5

	x			
1	2	3	4	5

3. It was easy to connect the 3D-print to the intrauterine tube using the snap-fit;

				x
1	2	3	4	5

				x
1	2	3	4	5

4. The applicator was easy to hold;

				x
1	2	3	4	5

	x			
1	2	3	4	5

5. It was easy to stabilise the applicator inside the phantom;

				x
1	2	3	4	5

	x			
1	2	3	4	5

Open questions

1. What do you like about the applicator design?

Smooth, ends outside the introitus	*Smooth, individualized fit*

2. What do you dislike about the applicator design?

Needle lock, and fixation clip did not work, and the spreading clip	*Sharp ends at ventral position. It is relative loose from the ovoid tube and that is problematic during insertion and removal. The 3d part ends in the vagina so packing is required this is less easy and the sharp ends will be in the lower vagina which can cause discomfort and injury.*

3. How can the design be improved for you/what feature would you like to be added to better meet your needs?

Leave out spreader, make sure the fixation clip works. Care should be taken for the guiding by hand of the needle outside the applicator during insertion.	*Rounded edges caudal and ventral. Better fixation of the ovoid tube to the 3d part.*

4. What functionality do you value the most in the design?

Individualized fit. Smooth design.	*Individualized fit smooth design, fixation of the guiding tubes is also easy to use.*

5. What is your greatest concern about the design?

Length if vaginal reference length is long. Amount of needles that can be used	*Insertion and sharp edges in the lower vagina*

6. For which specific patients would you choose this applicator design

As many patients as possible. This depends on local anatomy	*Those that benefit from individualized needle positions. Tumor extension in the vagina might be difficult to cover when disease extends to lower vagina in advanced disease. Also needle coverage ventral is difficult.*

7. Option for additional feedback:

Point for discussion is ease of reconstruction for both applicators	

B. System Usability Scale

The System Usability Scale (SUS) provides a 'quick and dirty', reliable tool for measuring the usability. It is a ten-item attitude Liker scale giving a global view of subjective assessments of usability. SUS has generally been seen as providing a type of high-level subjective view of usability and is thus often used in carrying out comparisons of usability between systems/products. Please indicate your opinion on the following statements: **strongly disagree (score 1) to strongly agree (score 5)**

	Applicator 1					**Applicator 2**				
1. I think that I would like to use his applicator frequently;					**x**				**x**	
	1	2	3	4	5	1	2	3	4	5
2. I found the applicator unnecessarily complex;	**x**						**x**			
	1	2	3	4	5	1	2	3	4	5
3. I thought the applicator was easy to use;					**x**				**x**	
	1	2	3	4	5	1	2	3	4	5
4. I think that I would need the support of a technical and/or medical person to be able to use this applicator;	**x**					**x**				
	1	2	3	4	5	1	2	3	4	5
5. I found the various functions in this applicator were well integrated;					**x**					**x**
	1	2	3	4	5	1	2	3	4	5
6. I thought there was too much inconsistency in this applicator;	**x**								**x**	
	1	2	3	4	5	1	2	3	4	5
7. I would imagine that most people would learn to use this applicator very quickly;					**x**					**x**
	1	2	3	4	5	1	2	3	4	5
8. I found the applicator very cumbersome to use;	**x**						**x**			
	1	2	3	4	5	1	2	3	4	5
9. I felt very confident using the applicator;					**x**				**x**	
	1	2	3	4	5	1	2	3	4	5
10. I needed to learn a lot of things before I could get going with this applicator;	**x**					**x**				
	1	2	3	4	5	1	2	3	4	5
	Total: 40 **SUS score: 40*2.5 = 100**					**Total: 32** **SUS score: 32*2.5 = 80**				

K.3. Radiotherapist-oncologist 3

Questionnaire

A. Design questions

5 questions about the design of the prototypes which will be answered using a 1-5 scale (1: strongly disagree, 5: strongly agree). The left table can be used to answer the questions for prototype 1, the right table for answering the questions for prototype 2. For example:

Strongly disagree				Strongly agree
	x			
1	2	3	4	5

Strongly disagree				Strongly agree
			x	
1	2	3	4	5

1. It was easy to insert and lock the IS needle;

1	2	3	4	5

			x	
1	2	3	4	5

2. It was easy to connect the 3D-print to the cervical stopper;

1	2	3	4	5

				x
1	2	3	4	5

3. It was easy to connect the 3D-print to the intrauterine tube using the snap-fit;

1	2	3	4	5

				x
1	2	3	4	5

4. The applicator was easy to hold;

1	2	3	4	5

				x
1	2	3	4	5

5. It was easy to stabilise the applicator inside the phantom;

1	2	3	4	5

				x
1	2	3	4	5

Open questions

1. What do you like about the applicator design?

Gemakkelijk te introduceren *Ovoid tube geintegreerd.*	*Gemakkelijk te introduceren*

2. What do you dislike about the applicator design?

Naald plaatsen met clipje erg stroef, zeker als er meer naalden moeten worden geplaatst. *Insertion tool niet bruikbaar*	*De bevestiging van de ovoid tube aan de spacer is wat los.*

3. How can the design be improved for you/what feature would you like to be added to better meet your needs?

Naalden inbrengen gaat moeizaam	*Iets vaster vastklikken van de ovoid tube in de spacer*

4. What functionality do you value the most in the design?

Gemak van inbrengen en mogelijkheid van individuele naaldrichting	*Gemak van inbrengen en mogelijkheid van individuele naaldrichting*

5. What is your greatest concern about the design?

geen	*geen*

6. For which specific patients would you choose this applicator design

patienten met een cervixcarcinoom met oppervlakkige vaginale uitbreiding, patienten waarbij je met de standaard naaldrichting niet mooi uitkomt. *Gezien aantal naaldposities minder geschikt voor zeer grote/uitgebreide tumoren*	*patienten met een cervixcarcinoom met oppervlakkige vaginale uitbreiding, patienten waarbij je met de standaard naaldrichting niet mooi uitkomt* *Gezien aantal naaldposities minder geschikt voor zeer grote/uitgebreide tumoren*

7. Option for additional feedback:

Aantral naaldposities beperkt	*Aantal naaldposities is beperkt, ook enkele plekken van de ring kunnen geen naalden uitkomen*

B. System Usability Scale

The System Usability Scale (SUS) provides a 'quick and dirty', reliable tool for measuring the usability. It is a ten-item attitude Liker scale giving a global view of subjective assessments of usability. SUS has generally been seen as providing a type of high-level subjective view of usability and is thus often used in carrying out comparisons of usability between systems/products. Please indicate your opinion on the following statements: **strongly disagree (score 1) to strongly agree (score 5)**

	Applicator 1					**Applicator 2**				
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	1	2	3	4	5	1	2	3	4	5
2. I found the applicator unnecessarily complex;		**x**				**x**				
	1	2	3	4	5	1	2	3	4	5
3. I thought the applicator was easy to use;				**x**						**x**
	1	2	3	4	5	1	2	3	4	5
4. I think that I would need the support of a technical and/or medical person to be able to use this applicator;	**x**					**x**				
	1	2	3	4	5	1	2	3	4	5
5. I found the various functions in this applicator were well integrated;					**x**					**x**
	1	2	3	4	5	1	2	3	4	5
6. I thought there was too much inconsistency in this applicator;	**x**						**x**			
	1	2	3	4	5	1	2	3	4	5
7. I would imagine that most people would learn to use this applicator very quickly;					**x**					**x**
	1	2	3	4	5	1	2	3	4	5
8. I found the applicator very cumbersome to use;		**x**				**x**				
	1	2	3	4	5	1	2	3	4	5
9. I felt very confident using the applicator;					**x**					**x**
	1	2	3	4	5	1	2	3	4	5
10. I needed to learn a lot of things before I could get going with this applicator;	**x**					**x**				
	1	2	3	4	5	1	2	3	4	5
	Total: 37					**Total: 39**				
	SUS score: 37*2.5 = 92.5					**SUS score: 39*2.5 = 97.5**				