NON-CONTAMINATED UTERINE MICROBIOME SAMPLING

for fertility research

Master Thesis
Integrated Product Design
Laura Heikamp

NON-CONTAMINATED UTERINE MICROBIOME SAMPLING

for fertility research

By

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Summary

The human microbiome and its relationship to several diseases is a new and evolving field of study. The uterine microbiome can be used to predict the chance of success of natural or assisted pregnancy. Possible contamination of the uterine microbiome during sampling hinders the ability to make conclusions about the possible relation between it and (sub)fertility. The sample is likely to get contaminated by the bacteria in the cervix, as the uterus has a low abundance of bacteria compared to the cervix.

A uterine microbiome sampling technique is created that can take a sample without contamination from the cervix. The designed sampler is a telescope layered product that is extending in the uterus of the patient, Figure 1. Two tubes protect a swab, and flexible valves connected to the tubes prevent contamination, Figure 2. The gynaecologist has control over the moment the product opens and the location of sampling. The sample can be used for modern microbiological research like Next-Generation Sequencing.

Functional prototypes of the sampling technique are tested in an In Vitro Test at Medical Microbiology and Infection Control Department of the Amsterdam UMC, location VUmc. The test delivered the proof of principle that the idea has potential to be able to take a non-contaminated sample.

Follow-up studies are recommended with a sampler specifically designed for research purpose. The goal of this test is on what the relation is of the uterine microbiome and (sub)fertility. Based on these results, the use case should be more specified to be able to design a sampler for commercial use. A commercial sampler is still for the future, but the proof of principle of the sampling technique shows that the idea has potential to sample the uterine microbiome without contamination.

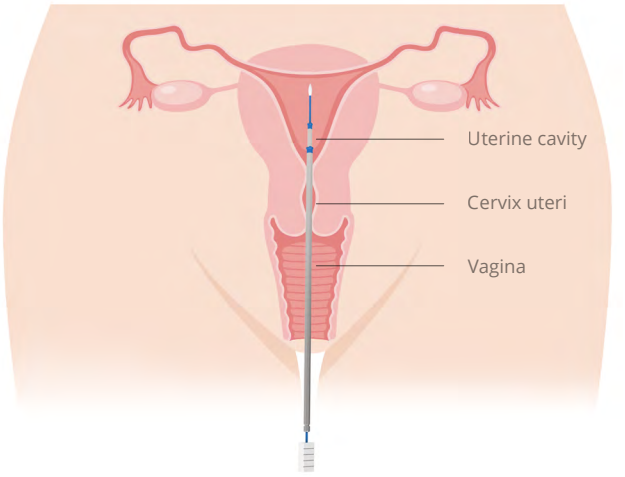

Figure 1: Sampler extending in the uterus

Figure 2: Sampler with protected swab

Preface

Before you lies my master thesis report, which is the final part of my Master of Science in Integrated Product Design of the faculty of Industrial Design Engineering at Delft University of Technology. The project has been focused on a medical topic to obtain the Medisign specialisation. This graduation thesis is a collaboration with IQ Medical Ventures and the Gynaecology department of the UMC Utrecht. The thesis describes the research I carried out to explore the possibilities of uterine microbiome sampling without contamination for fertility research. Prof. Dr. Ir. Goossens and Dr. Ir. Flipsen of Delft University of Technology supervised the project.

Throughout this project, I have learned to design with and for medical professionals. The topic of the uterine microbiome is still novel but is getting more attention in the medical field. From a design engineering perspective, this topic is not yet explored in depth. I believe that this combination of a medical and design engineering perspective fits the final chapter to my career at the TU Delft.

I want to express my gratitude to everyone involved in supporting me. Firstly, Richard Goossens for his sincere support, pleasant positive feedback and enthusiasm throughout the project. Bas Flipsen for his guidance during the project, keeping me focused when needed and for being open-minded from a non-medical perspective. Also, I would like to express my gratitude to Johan Remmerswaal for his critical but practical feedback, letting me feel welcome at IQ Medical Ventures and providing expertise when needed from his extensive network. My gratitude goes to Mark Hans Emanuel for introducing me to the field of gynaecology, his never-ending enthusiasm and connecting me to Medical Microbiology which elevated my project to a next level. I want to express my gratitude to Dries Budding and Heleen Schuster of the Medical Microbiology and Infection Control Department of the Amsterdam UMC, location VUmc, for providing me with everything I needed for the test and their expert review on my project. Lastly, I would like to express my gratitude to my family and friends for supporting me each in their own way during this project and really throughout my whole studies and life.

L.M.J. Heikamp
Delft, February 2019

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Glossary

The terminology is placed in alphabetic order:

Cervix (uteri)	the canal from the uterine cavity to the vagina
Colonisation	the presence and multiplication of microorganisms
Contamination	presence of unwanted material or microorganisms in a sample or place
Embryo	the early stage development of a multicellular eukaryotic organism
Endometrium	the inner layer in the uterine cavity
Fallopian tube	a tube from the ovaries to the uterus for transport of sperms or an embryo
Gram-negative	bacteria that give a negative result to the Gram stain test to classify bacteria based on their cell wall
Gram-positive	bacteria that give a positive result to the Gram stain test to classify bacteria based on their cell wall
Hysteroscopy	procedure to examine the inside of the uterus
Infertility	a misfunction of the reproductive system which results in the inability of pregnancy
Microbiome	the combination of microorganisms like bacteria, fungi, archaea and viruses
Multipara	woman who gave birth to one or more children
Nullipara	woman who never gave birth to children
Ostium	an opening into a vessel or cavity of the body
Ovaries	organ that produces eggs and hormones
Speculum	medical device to spread the vagina for gynaecological purposes
Sterile	free from bacteria or other living microorganisms
Subfertility	reduced fertility with prolonged time of unwanted non-pregnancy for over a year
Transcervical	through the cervical opening of the uterus
Uterine cavity	triangular collapsed space in the body of the uterus
Uterus	organ important for the female reproductive system where an embryo can implant
Vagina	muscular canal extending from cervix uteri to outside the body

The abbreviations are placed in alphabetic order:

16s rRNA	16Svedberg ribosomal ribonucleic acid: species-specific sequences used for NGS technique for bacterial identification
ART	assisted reproductive technology: medical procedures used to treat infertility
CE	Conformité Européenne: certification mark within Europe
CFU	colony-forming unit: a unit to estimate the number of viable bacteria or fungal cells in a sample
FMEA	Failure Modes and Effects Analysis: process analysis tool for identifying all possible failures
ICSI	intracytoplasmic sperm injection: ART technique in which one sperm cell is selected and brought into an egg
IVF	in vitro fertilisation: ART technique in which one egg is in contact with many sperm cells
MDR	Medical Device Regulations: regulations that replace EU's current Medical Device Directive and Directive on active implantable medical devices
NGS	next-generation sequencing: technique for analysing microorganisms
RPN	Risk Priority Number: multiplication of the severity, occurrence and detection of a failure mode in an FMEA
SBA	sheep blood agar: a growth medium with nutrients used to culture microorganisms
TSB	tryptic soy broth: a culture broth to grow aerobic bacteria

1. INTRODUCTION

In the introduction, the topic of the graduation thesis and the collaboration partners, IQ Medical Ventures and the gynaecology department of the UMC Utrecht, are introduced. The Problem Definition, design goal and Design Vision Statement are shortly discussed to define the scope of the thesis. Finally, a readers guide for the rest of the document is explained together with the used methods.

Prologue

The human microbiome and its relationship to several diseases is a new and evolving field of study (Cho & Blaser, 2012). Microbes in for example the gut can tell something about the health of a person. In the field of gynaecology, it has been discovered that the vaginal microbiome has a predictive character for the spontaneous occurrence of pregnancy or if the implantation of an embryo in Assisted Reproductive Technology (ART) is likely to succeed (Mitchell et al., 2015). Other research shows there is a continuum of the vaginal microbiome and the microbiome in the uterine cavity (Verstraelen et al., 2016; Baker, Chase, & Herbst-Kralovetz, 2018). Figure 3 shows the genital organs of importance for this graduation thesis. Since implantation will eventually take place in the uterine cavity, this microbiome is the most interesting to understand. Currently, there is no sampler available to take a sample from the uterine cavity without contamination of the cervix uteri. This makes it also hard to draw conclusions about the relation between the uterine microbiome and possible other gynaecological disorders (Benner, Ferwerda, Joosten, & van der Molen, 2018). The development of this sampling technique for the uterine cavity without contamination of the vagina and cervix uteri will be the focus of this graduation thesis. Appendix 1 shows the initial graduation proposal as approved by the board of examiners.

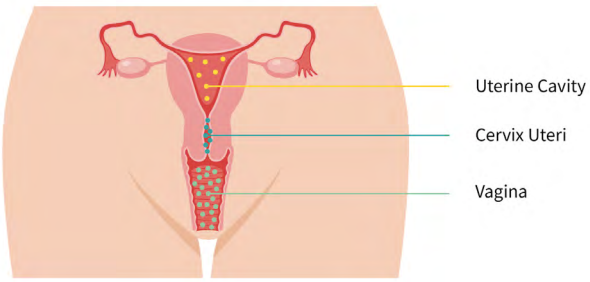


Figure 3: Genital organs of importance for graduation thesis

IQ Medical Ventures

The graduation assignment is in collaboration with IQ Medical Ventures, a medical incubator located in Rotterdam. The main focus of IQ Medical Ventures is to overcome the traditional drawbacks of licensing technology to the broader medical industry. IQ Medical Ventures is a part of RHO-dam Ventures BV, in which each company has a different focus on commercialising technology by licencing, venturing or financing the technologies (Figure 4). The company has different IQ-companies with each of them having a different medical field of interest. Currently, the company has launched four products on the market in different medical industries of which one of them is sold to and marketed by a USA based multinational.

UMC Utrecht Gynaecology

In this graduation assignment, the gynaecology department of the University Medical Centre Utrecht has a guiding role. The initial problem description is from Prof. Dr. Mark Hans Emanuel, a gynaecologist who has worked with IQ Medical Ventures and Delft University of Technology before. Emanuel is specialised in the uterine cavity, is operative in the University Medical Centre Utrecht and is a professor at University Hospital Ghent in Belgium. This graduation assignment is executed with him as an expert in the uterine cavity and the handling of medical gynaecological instruments. Emanuel is not only gynaecologist but also has experience with the development of medical devices and holds several patents for gynaecology products.

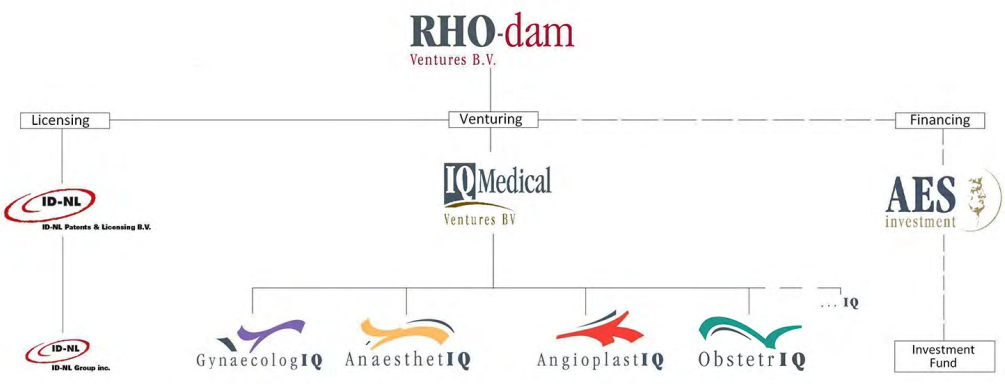


Figure 4: Overview IQ Medical Ventures

Problem definition

Research shows (Verstraelen et al., 2016; Baker et al., 2018) that the uterine microbiome has a predictive value for the chance of success of natural or assisted pregnancy. There is currently no device available that can take a sample of the uterine microbiome, without contamination (or any another alteration) of the uterine microbiome. Contamination is an important issue because the vagina and cervix uteri contain approximately 100-10.000 times more bacteria than the uterus (Chen et al., 2017; Mitchell et al., 2015). A little contamination results in a significant sampling error. Therefore researchers are still not able to conclude when the microbiome of a uterus is considered as 'healthy' or not and if probiotics or antibiotics can alter the microbiome. Subsequently, because researches do not have the right sampling technique, gynaecologists are still not able to analyse the microbiome for the diagnosis of fertility issues. The problem definition is stated in the text block below.

Research into the relationship between other gynaecological disorders and the microbiome has the same impediment because no sampler is available yet that can take a non-contaminated sample. There may be a link between the microbiome of women with, for instance, post-menopausal bleeding disorders or polyps. This graduation thesis is mainly focused on fertility research because this is the field that currently shows the most evidence in the literature for the link of the uterine microbiome and fertility. Nevertheless, it is essential to keep in mind that this product could be of high importance for other gynaecological research as well.

Graduation assignment

The aim of this graduation thesis is to deliver a proof of principle for a uterine microbiome sampler. The design goal is summarised in the text block below. Next-Generation Sequencing (NGS) makes it possible to analyse a microbiome (Franasiak et al., 2016), but for this, a sample needs to be taken and transferred to this device to be able to examine it. Unfortunately, with the current technology it is not possible to have a real-time test in the uterus. Because there is currently no device available that can take a sample without contamination (or other alteration), further research is stagnating. Therefore the primary importance of this assignment is to be able to prove if it is possible to take this non-contaminated sample. With an In Vitro Test, the design of a sampler will be evaluated. Based on these results, a proposal for a sampler for research purpose will be made. The Design Vision, as stated below, is of importance during the transition towards a sampler for research or commercial purpose.

This thesis will focus on the importance of the microbiome for fertility research and treatment because this has the most promising literature. After the generation of a concept, further research is needed for the clinical evidence of the relationship between the uterine microbiome and subfertility. If this research is further progressed, a commercialised sampler and research method needs to be developed to make the product available in the gynaecological industry. The development towards a commercialised sampler is out of the scope of this master thesis.

Problem Definition:
There is currently no medical device for taking a non-contaminated sample of the uterine cavity to examine the microbiome. This hinders research concerning the relation of the uterine microbiome and (sub)fertility.

Design Goal:
Design a sampler for taking a sample of the uterine cavity without contamination for research concerning the relation of the uterine microbiome and (sub)fertility.

Design Vision Statement:
The sampler should be able to take non-contaminated material of the uterine cavity to examine the microbiome, while having the highest usability for the gynaecologist, being the most patient-friendly and being suitable to sample material for modern microbiological research methods like Next-Generation Sequencing.

Readers guide

The chapters of the project are based on the phases of the Waterfall model. This model is often used in the software engineering (MaRS, 2018), but is slightly adjusted for this project (Figure 5). Figure 6 shows the readers guide with an overview of the process of the thesis. In this overview are also the used (design) methods of each phase shown that are explained in Appendix 2.

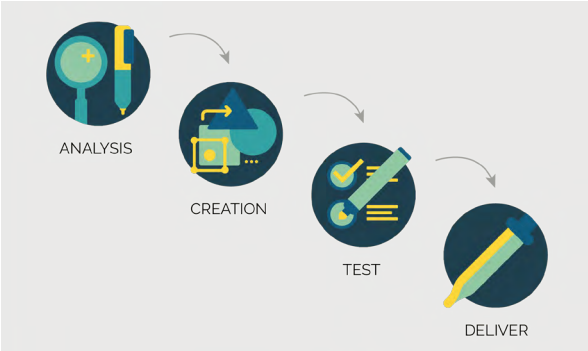


Figure 5: Phases based on the Waterfall model (MaRS, 2018)

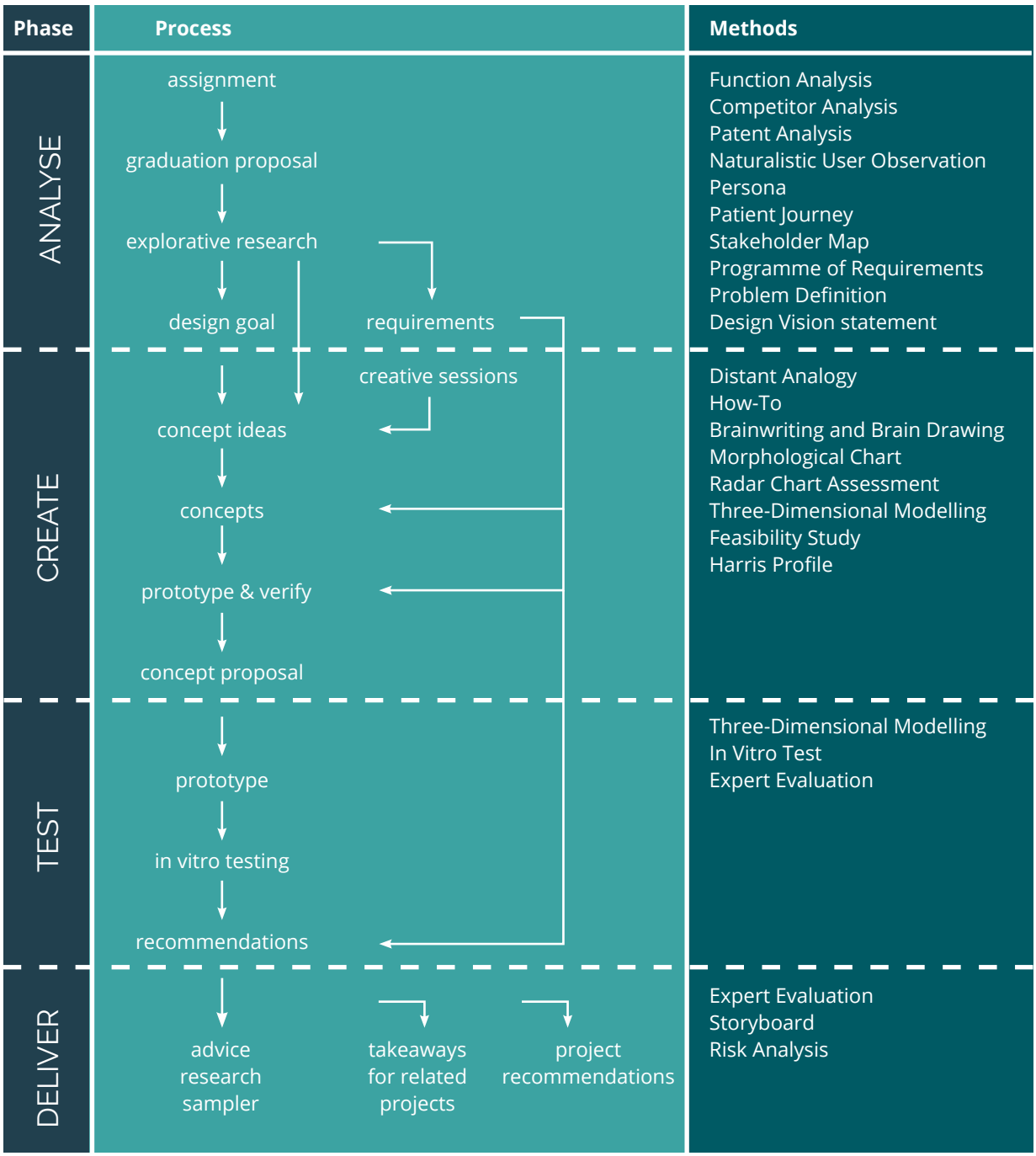


Figure 6: Readers guide of phases, process and methods

2. ANALYSIS

The analysis is divided into five sections. In the medical analysis, the medical background and researches are explained. In the product analysis, the functions of the product, inspirational products and similar products are analysed. The user analysis illustrates the target group and ergonomics of the users. The system analysis creates an overview of the environment in which the product will be operating in and what kind of impact the product can have. Finally, this phase concludes in a summarising infographic, a list of requirements and a defined scope of the project.

2.1 Medical analysis

Introduction

The medical analysis introduces the medical background of the thesis. The female reproductive system and subfertility are shortly explained. The role of the uterine microbiome and the influence of contamination are of importance for the main functionality of the product. In the next section of the analysis, the product will be further analysed.

Female reproductive system

The female reproductive system is made up of the internal and external sex organs, Figure 7 and Figure 8, which are focused on the reproduction of the human species (El-Mazny, 2016; Rogers, 2011). The organ that is of importance for this project is the uterus (Sosa-Stanley & Bhimji, 2018; Ellis, 2011). It exists of two parts: the body and the cervix. In the cavity of the body, the implantation of an embryo can take place (Sosa-Stanley & Bhimji, 2018). For this project, a sample of the endometrium of the uterine cavity will be taken to analyse the bacteria in it. The data collected from this sample is important for the implantation of an embryo. Most images show the uterus as a real cavity, while in real life, the walls are more collapsed towards each other. The entrance to the uterine cavity is via the vagina and the cervix. During a gynaecological intervention, the vaginal walls can be separated by a speculum to give entry and vision to the external ostium (Ellis, 2011), Figure 9. The cervix is a canal with a small diameter and the nerves in the muscle tissue can cause intense pain when something dilates the cervix. Figure 10 shows the shape of a normal external ostium of the cervix for nullipara and multipara. Through this ostium, the sample of the endometrium will be taken.

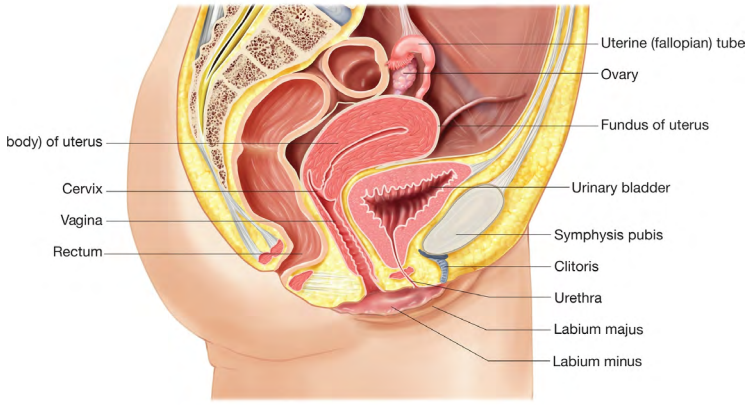


Figure 7: Lateral view female reproductive system (Human Body Anatomy, n.d.)

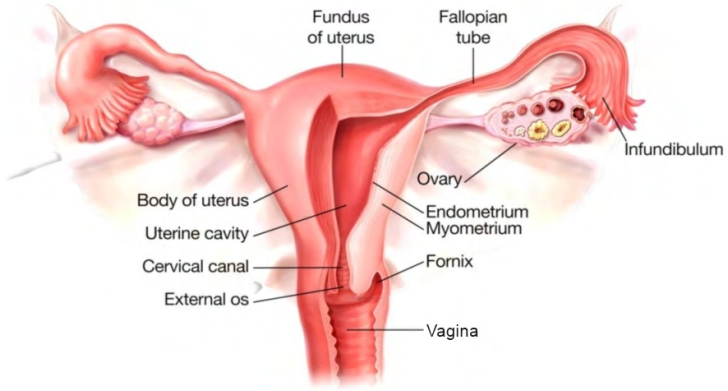
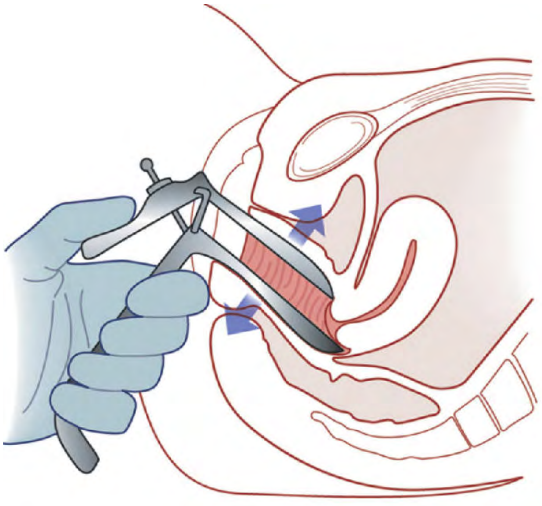


Figure 8: Anterior view female reproductive system (Human Body Anatomy, n.d.)

The fertile years of a woman start during her puberty and end with the menopause. Each month she has her menstrual cycle and can get pregnant (Rogers, 2011). However, becoming pregnant is not an easy and natural process for everyone. In the Netherlands, approximately 80% of couples become pregnant within one year having unprotected sexual intercourse. If this is not the case, the term subfertility is used. Eventually, 5% of the Dutch couples are not able to conceive (Schipper, 2015) and the term infertility is used. The human fertilisation process is a complex system, and infertility can have a lot of different causes (Vrij-Mazee, Liedtke-van Eijck, Eskes, & Seumeren, 2018). While for most of these women a diagnosis will give more information, for 10% of couples the reason behind infertility is unknown. For many more, it is unknown why they are subfertile. Therefore this project is initiated, to hopefully be able to give more answers to those couples.



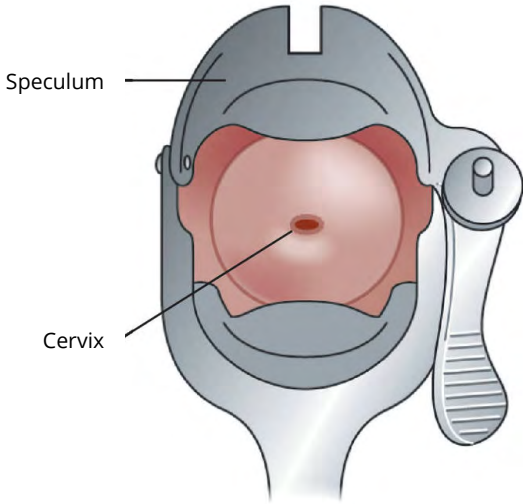


Figure 9: Speculum inserted in vagina (Farlex, 2018)

A couple that is having issues with becoming pregnant, often go to a gynaecologist or fertility specialist at a hospital or institution where several medical analyses take place (UMC Utrecht, n.d.; Solvo, 2018). Depending on the diagnosis, there are different medical solutions available (Mayo Clinic, 2018; NICHD, 2017), for example, surgery or ART. In Vitro Fertilization (IVF) is a commonly used procedure of ART, and most couples need 2 to 3 cycles of assisted embryo implantation before pregnancy succeeds (Freya, n.d.). Appendix 3 explains more about the anatomy of the female reproductive organs, the menstrual cycle, pregnancy, subfertility and the medical paths for this.

Role of the uterine microbiome

The microbiome is a collection of all microorganisms living in and on the human body (Turnbaugh et al., 2007), like eukaryotes, archaea, viruses and bacteria. The clinical relevance of the microbiome is that our microbiome correlates with several disorders and manipulation of the microbiome could potentially be used to treat it (Ettinger, MacDonald, Reid, & Burton, 2014). Since a few years, the uterine microbiome is analysed and is associated with implantation failure, pregnancy loss, and other gynaecological and obstetrical conditions (Moreno & Franasiak, 2017; D'Ippolito et al., 2018; Benner et al., 2018).

> *"An abnormal endometrial microbiota has been associated with implantation failure, pregnancy loss, and other gynecological and obstetrical conditions"* (Moreno & Franasiak, 2017)

Figure 10: External ostium (Reusch et al., 2011)

For almost 100 years medical specialists thought a healthy uterine cavity should be sterile. This statement is challenged since the mid to late 1980s by using culture-dependent methods (Heinonen et al., 1985). The introduction of the NGS technology in 2005 made it possible to further research the human microbiome (and thus the uterine microbiome) by being able to thoroughly analyse a sample (Baker et al., 2018; Behjati & Tarpey, 2013). There is some disagreement between researchers on where a sample should be taken and whether the sample location is even important.

The method for analysing the human microbiome is called 16Svedberg ribosomal ribonucleic acid (16S rRNA) sequencing. It focusses on identifying and comparing bacteria and is used for research into the uterine microbiome (Benner et al., 2018). Dries Budding (personal communication, October 02, 2018; July 06, 2018), founder of the IS Pro technique, explains that with the IS Pro technique the 16S-23S interspace region is analysed. Within 5 hours the bacteria in a microbiome are analysed down to one bacterium. Therefore no minimum size of a sample is needed. A normal endometrial biopsy provides enough tissue for the IS Pro (Budding, 2018). More information about the role of the uterine microbiome and how to research it is available in Appendix 4 and the expert meeting of Appendix 5.

Influence of contamination

Nowadays we have more technologies to analyse the uterine microbiome, but gynaecologists are not really able to sample the microbiome for diagnosis and treatment (Benner et al., 2018). Available studies often have issues with possible contamination of the vaginal and cervical microbiome during transcervical collection (Baker et al., 2018; Walter-António et al., 2006). Contamination refers to the non-intended introduction of microbes at a specific place (Journal of Pharmaceutical Microbiology, 2018). The most interesting studies of the uterine microbiome and contamination prevention are described in Figure 11, based on the case studies of Baker et al. (2018). A little contamination results in a significant error in the sample, because it is estimated that the vagina and cervix have 100 to 10.000 times more bacteria than the uterus (Chen et al., 2017; Mitchell et al., 2015). So with current research methods and instruments scientists are still not able to make solid conclusions. As researchers request, a new product and method are needed to be able to research the microbiome to understand what is happening in the uterus (Baker et al., 2018). If this is possible, gynaecologists will hopefully be able to treat subfertility issues with probiotics, antibiotics or dietary solutions that could potentially change the microbiome (Ettinger et al., 2014).

Research	Sample type	Contamination prevention
Mitchell et al. (2015)	Endometrial swabs from excised uterus	Sample collected only when an intracervical manipulator was not needed
Franasiak et al. (2016)	Distal 5 mm of IVF catheter tip	Formable outer sheath advanced under ultrasound guidance
Verstraelen et al. (2016)	Tao BrushTM IUMC Endometrial Sampler	Cervical surface rinsed with antiseptics and disinfectants. Sampling brush protected in Tao Brush
Fang et al. (2016)	Endometrial swabs	Vaginal and cervical canal disinfected. Endometrial swabs with sleeves
Khan et al. (2016)	Seed swabs	Seed swab was inserted under visual control into the uterine cavity
Moreno et al. (2016)	Transcervical catheter	Suction was dropped at the entrance of internal ostium
Walther- António et al. (2016)	Swabs following hysterectomy	-
Miles, Hardy, & Merrel (2017)	Endometrial and other swabs taken post-hysterectomy	-
Chen et al. (2017)	Nylon flocked swabs	-

Figure 11: Overview research uterine microbiome, based on Baker et al. (2018)

Figure 12 provides an illustration of the influence of contamination. The cervix is a high-load environment (a high concentration of bacteria), and the uterus is a low-load environment (a low concentration of bacteria). The exact concentration of bacteria is currently unknown. Therefore an estimation is made based on research of Chen et al. (2017) and Mitchell et al. (2015). In the example, the cervix has a concentration of 10^8 and the uterus a concentration of 10^4. As an illustration of possible contamination, 10^{-3}ml from the cervix is contaminating a sample of 1ml of the uterus. This contamination of just a thousandth of a millilitre results in 10 times more bacteria in the sample from the cervix than from the uterus. Therefore possible contamination of the cervix is a significant hurdle in research to the uterine microbiome because researchers do not know to what extent the sample may be contaminated.

"However, the study of the endometrial microbiota, as with other low-biomass microbiota, presents important hurdles because, due to the small amount of starting material, they are easily contaminated by exogenous bacterial DNA. [...] This contaminant DNA may affect the results of both 16S rRNA gene sequencing and shotgun metagenomic analysis. " (Moreno & Simon, 2018)

"Background bacterial contamination critically affected the result" (Kyono, Hashimoto, Nagai & Sakuraba, 2018)

Conclusion

The text box to the right provides a summary of the most important requirements of this medical analysis. These requirements are of importance for the medical functionality of the product and provide a starting point for the next steps in the research procedure. In the final section of the analysis phase, the requirements are listed.

Derived requirements:

- The product must be able to take a non-contaminated transcervical sample of the microbiome of the uterine cavity.
- The product must collect a sample that is large enough for 16S rRNA sequencing.

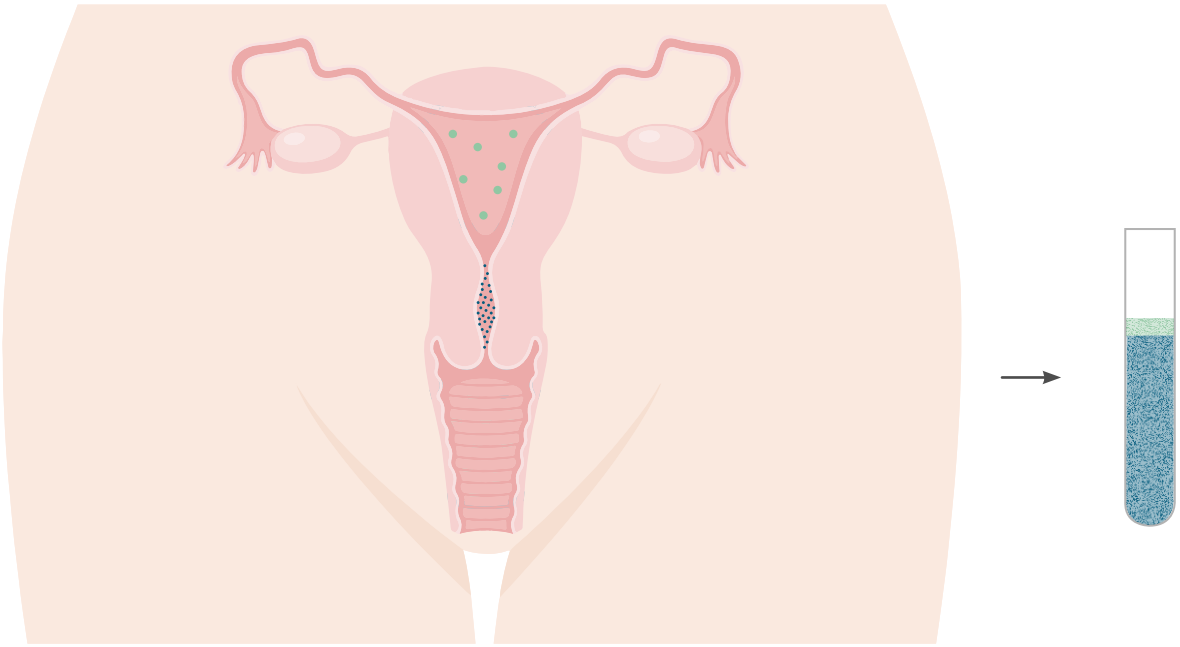


Figure 12: Contamination of cervix in the sample

2.2 Product analysis

Introduction

The product analysis presents the functionality of the product. The main functionality, derived from the medical analysis, is further explored. Interesting products currently on the market are analysed. In the patent analysis are patents analysed for inspiration and as a novelty study for the product. Finally, the look and feel of the product is shortly discussed. In the next section of the analysis, the product will be linked to the users that will be using the product: the gynaecologist and the patient.

Similar procedures

Since a few years, several procedures have been developed to research the probability of a successful pregnancy. Figure 13 shows an overview of these products and procedures. Experts are still sceptical to some of these products and procedures. The main conclusion is that none of the current products on the market focus on the analysis of the microbiome of the endometrium.

There are currently products on the market that fulfil a slightly similar (sub)function. These are presented in Appendix 6. Samplers with a brush or manual suction are also interesting for their dimensions. It shows that similar products have a diameter of 2,6 to 4 mm. The length of the total device is approximately 250 to 260 mm to be able to take a transcervical sample of the uterus. 50mm of the total length is for the handling of the device.

Function analysis

A Function Analysis is made (Figure 14), based on medical analysis, several observations (Appendix 5) and expert meetings (Appendix 7). The primary function is broken down in several sub-functions and will be the basis of the functional properties in the Programme of Requirements. Some of the sub-functions are not a function that the actual device needs to fulfil but could be, for example, the instruction guide or packaging.

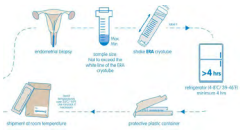
Procedure	Explanation procedure	Visual procedure
ERA (Igenomix, 2018) of Igenomix, ES: Low pressure uterine sampler	The Era test uses a Pipelle to take a sample of the endometrium. This sample will be evaluated whether or not the endometrial lining is prepared to accept an implanting embryo. Igenomix (personal communication, September 17, 2018) explains that contamination of the cervix is insignificant because they do not focus on the bacterial consistency.	
ReceptIVFity (2018) of ARTPred (2018), NL: Vaginal microbiome swab	ReceptIVFity is a vaginal microbiome sampling procedure which checks the probability chance of IVF succession. The bacterial RNA of a vaginal swab is analysed in a laboratory, and the patient will receive the results from the doctor. This result of a successful IFV prediction can be high (52,6%), middle (23,6%) or low (5,9%).	
VivoPlex (n.d.), UK: Sensors intrauterine	The Vivoplex is a concept from the University of Southampton, which is not available on the market yet. This product uses small biometric sensors to measure real-time the dissolved oxygen, pH and temperature in the uterus of a woman with fertility issues. *"If the pH levels are not in the right range there might be something wrong with the microbiome"* (Spencer, 2018).	
Fertilome (2018) of Celmatix (2018), US: Blood test DNA	The Fertilome test checks the patient's blood for DNA markers that are associated with certain reproductive health conditions. Based on these results, the patient can make more well-founded decisions about when to start treatment, how to proceed after an unsuccessful cycle or whether to consider to freeze eggs or embryos.	

Figure 13: Similar procedures

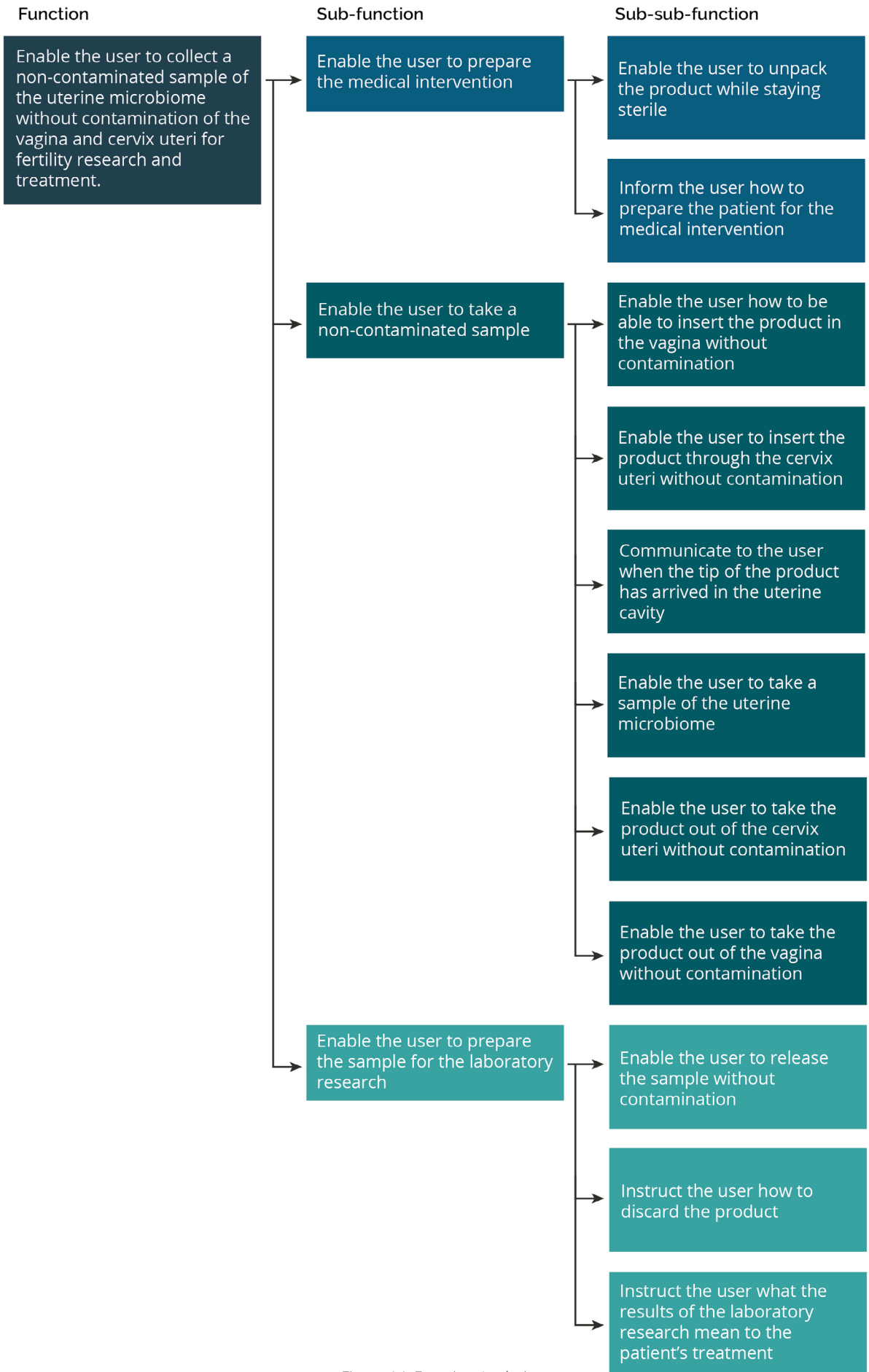


Figure 14: Function Analysis

Patent analysis

Interesting products currently on the market are analysed. In the patent analysis patents are analysed for inspiration and as a novelty study for the product. Appendix 8 shows more of the Patent Research. A full-text search through world-wide published patents is executed, with key-words such as 'uter*', 'microbiome', 'microbiota', 'sampl*', 'swab', 'preventing contamination', etc. Figure 15, Figure 16 and Figure 17 show the three main inspirational examples.

Look and feel

The product will be designed for the gynaecology department of a hospital. Therefore the product should fit this context, just like the inspirational products analysed in a Competitor Analysis in Appendix 6. The product is expected to look patient-friendly during this stressful period of fertility research (Baghianimoghadam et al., 2013), but this is not extremely important according to Prof. Dr. Mark Hans Emanuel (user observation, Appendix 5). First, the patient does not notice the instruments much, because of their position in the gynaecological chair. Second, the gynaecologist handles and prepares the instruments at a low level to make sure the patient does not notice the instruments that much. Third, most gynaecological instruments are not patient-friendly looking because of their large size, metal look and painful association. Therefore the look and feel of the product is not the primary importance.

Conclusion

In the text box is the conclusion of the product analysis summarised in requirements focused on the functionality of the product and its functionality compared to competitors. These requirements are added to the derived requirements from the medical analysis. In the next section, the sampler will be linked to the users.

Derived requirements:

- The product must prevent contamination with the cervix, vagina or any other part during preparing, inserting, sampling, pulling out and releasing in a test tube.
- The product must be disposed after one-time use.
- The product needs to be able to release the sample into a test tube of the hospital for further research.
- The product needs to be able to be patented by IQ Medical.

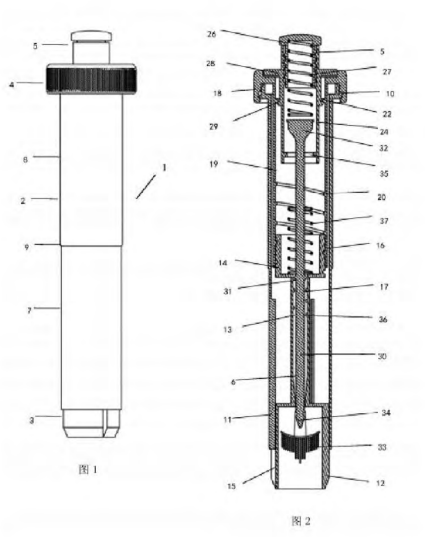


Figure 15: CN Patent application 2016/104622518 Cervical cell sampler with a pen-like system

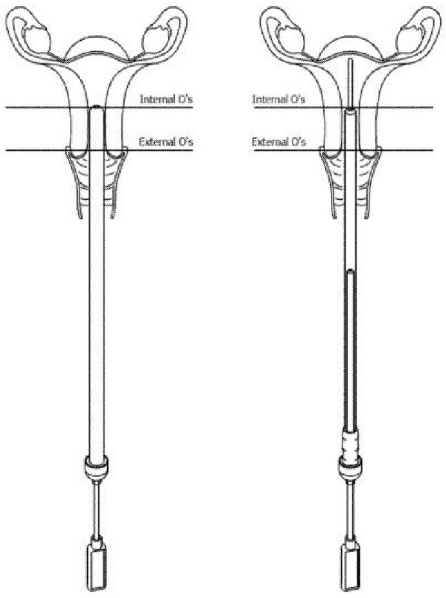


Figure 16: US Patent application 2018/9730679 Multiple layered drug delivery system

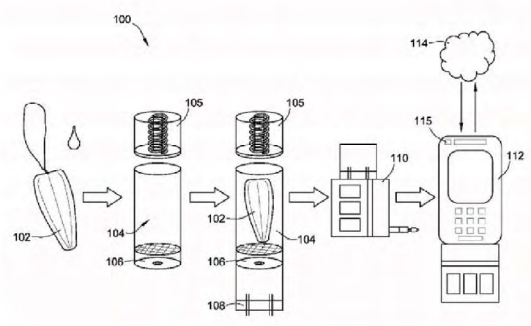


Figure 17: WO Patent Application 2017/180909 Vaginal sampler, including the extraction and an assay cartridge

2.3 User analysis

Introduction

The user analysis focuses on the primary users of the product. The target group is the gynaecologist, but the patient is of importance as well. These are both observed to generate a Patient Journey in which the product is involved. Finally, the ergonomics are analysed to understand the physical ergonomics of both users and the cognitive ergonomics of the gynaecologist. In the next section of the analysis, the users and the product will be linked in a system.

Target group

The main target group of this product is the gynaecologist. The gynaecologist is the one using the product and needs to know how to handle it. Nevertheless, the patient needs to be included as well, because the product will be used inside her. Therefore it needs to fit her body and expectations while maintaining the focus on treatment by the gynaecologist and patient safety. In Figure 18, Personas are presented to have an overview of the main users. Observations at the UMC Utrecht are executed during hysteroscopic procedures (Appendix 5), to be able to generate the Personas.

The Personas are focused on subfertile couples, to generate a focus in the research. The target group can be expanded when research shows more about the link between the uterine microbiota and other gynaecological disorders.

GYNAECOLOGIST

- 25-67 years old
- (assistant) Gynaecologist or fertility doctor
- Work at a hospital or medical institution
- Educated at university
- Various household composition
- Caring character

MEANING
- Helping couples with pregnancy
- Give everyone a chance for family
- Provide good advice

FOCUS
- Research vs practice
- Best technology for patient
- Patient safety comes first

RESOURCE
- Colleagues
- Congresses
- Availability at hospital

PATIENT

- 18-50 years old, mostly with partner
- No child or wish for more children
- Various education/jobs
- Enjoys being with family and friends
- Not pregnant within a year
- Under the care of a gynaecologist/fertility doctor

MEDICAL
- Subfertile with unknown reason
- Different medical research

RESOURCE
- Information from gynaecologist
- Reads fertility blogs
- Talks to family and friends

GOAL
- Become pregnant
- Least hassle
- Futurize life with a child

Figure 18: Personas gynaecologist and patient

User observation

Ten user observations are executed at the gynaecology department of UMC Utrecht. Five observations took place at hysteroscopy consults on May 15th, 2018. During these Naturalistic User Observations the patient, a gynaecologist and gynaecologist under training were observed. Five other observations took place at hysteroscopic surgeries on October 11th, 2018. During these observations the patient, a gynaecologist and two gynaecologists under training were observed. Other medical experts present during the surgeries were not observed. Appendix 5, shows a further explanation of the observation goals, trigger questions, experts, patients, layout and main insights. Figure 19 contains a summary of the most important insights.

Hysteroscopy observation	**Hysteroscopic surgery observation**
There is a gap between the collaboration of industry, research and hospitals regarding the development of products because each partner has a different core business.	The patient does not notice the instruments that much, because of their position in the gynaecological chair.
"To what extent is it true what is currently known about the uterine microbiome?"	Most of the instruments are available in one or multiple sizes. If there is only one size, the product is often flexible, or a patient needs to be dilated beforehand.
Visual understanding of anthropometric dimensions and orientation of female genital organs is needed to understand the use context of the product.	Contamination needs to be prevented by a foolproof device. The procedure needs to be easy to understand, mainly because of the lack of time and technological understanding.
The cause of several gynaecological disorders and the required treatments are still unknown, which is also often the case for subfertility.	*"There are many 'scary looking instruments' on gynaecology, while some only hold a sterile gauze."*
There is currently no non-contamination sampler for the uterine microbiome available in hospitals, while gynaecologists have heard of the possible relevance of use.	The gynaecologist prefers a recognisable design and way of handling because they think it will improve acceptance of a new product amongst other gynaecologists.

Figure 19: Main insights observations

Patient journey

The future patient and gynaecologist have several touchpoints with each other and the product. In Figure 20 a possible Patient Journey is drawn up, based on the observations at the UMC Utrecht and quotes from subfertility blogs. The top part of the figure explains the journey. The bottom part provides a visualization of the possible emotional path of the patient, based on the story of Anisia of Infertility is Humility (2018). In this path are the quotes from subfertility blogs located to a particular moment. In the figure several paths are lined out, based on the result of the microbiome test and the treatment plan. The Patient Journey is focused on subfertile couples. Other journeys can be created when research shows more about the link between the uterine microbiota and other gynaecological disorders.

Quote 1

"Unfortunately the ReceptIVFity test resulted in an unfavourable profile, which shows a pregnancy rate of success for the second IVF of only 5%. I do not know what to do with it. I feel blank, angry, I do not get it. How is this possible?!"
(Translated from Grote Kleine dromen, 2018)

Quote 2

"Six-and-half year trying, two surgeries, two miscarriages and way more. But we made it. We are pregnant. And this time everything will be fine. I know it for sure."
(Translated from Patty, 2018)

Quote 3

"So many questions and decisions to make. So much insecurity in already a period of insecurity. A feeling of freedom to do what I want to do and do not. But do I know what I want? But when do you know what is good to do?"
(Translated from Floor, 2018)

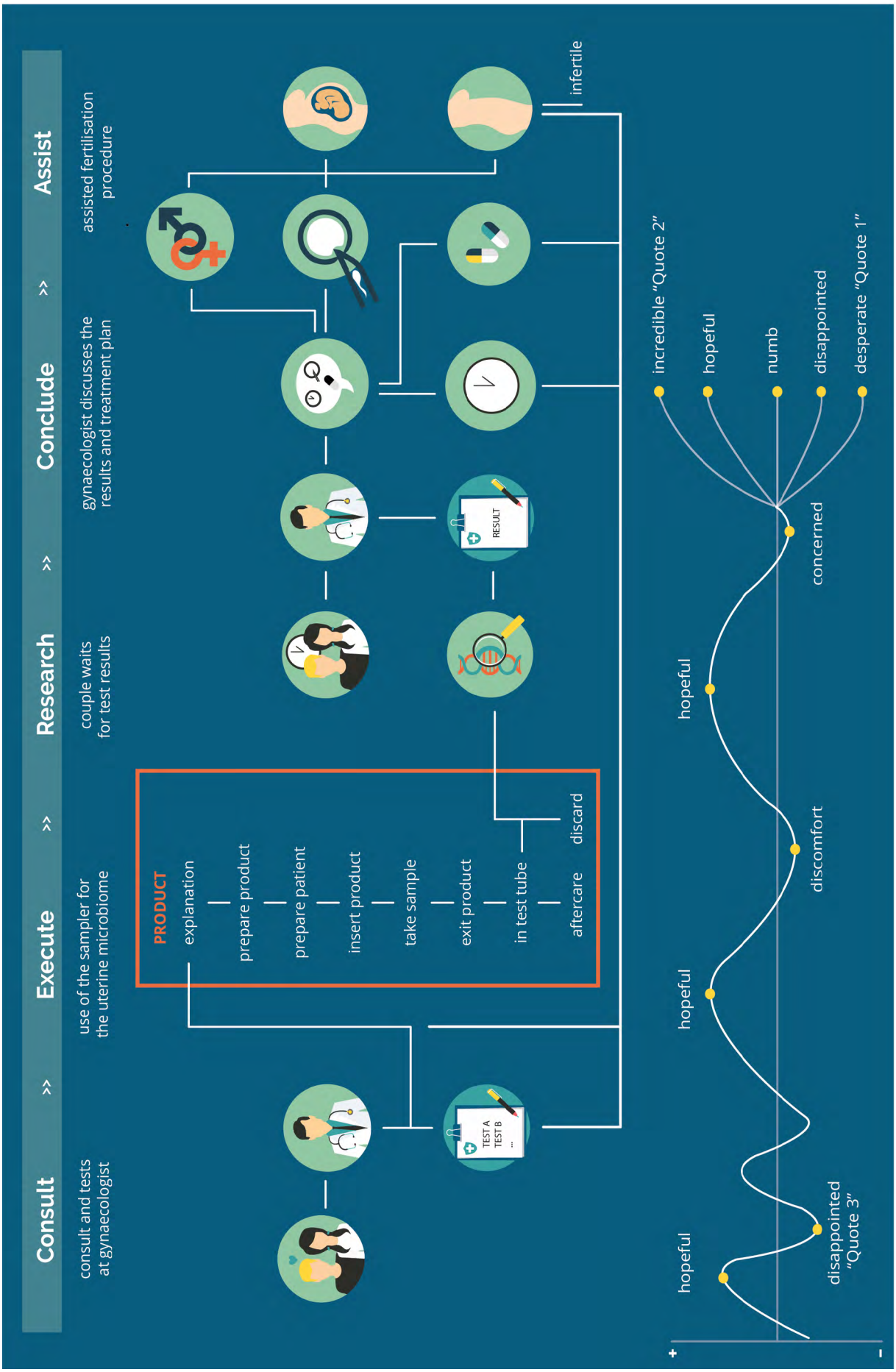


Figure 20: Patient Journey

Physical ergonomics

The product will be used in the uterus of the patient, and therefore the anthropometric features of the uterus and the path towards are essential for the design. The focus will be on the dimensions of the female reproductive organs and not on other dimensions because the patient is positioned in a gynaecological chair. The measurements from Figure 21 come from several studies in which often the mean is used. Since each research used different methods and way of noting their results, this figure is just a general overview of the anthropometric dimensions.

The dimensions are not the only essential features of the female reproductive organs. The shape of the uterus and the cervix are important as well. Figure 22 shows the shape of most of the uteri in which the uterus is anteverted (tipped forward) and anteflexed (fundus is pointing forward relative to the cervix), Volker (2018). As everyone's body is different, some uteri can be retroverted (tipped backwards) and retroflexed (fundus is pointing backwards).

The product will be used by the gynaecologist by hand, for this product several dimensions are of importance. These dimensions and biomechanics of the hand are presented in Appendix 9.

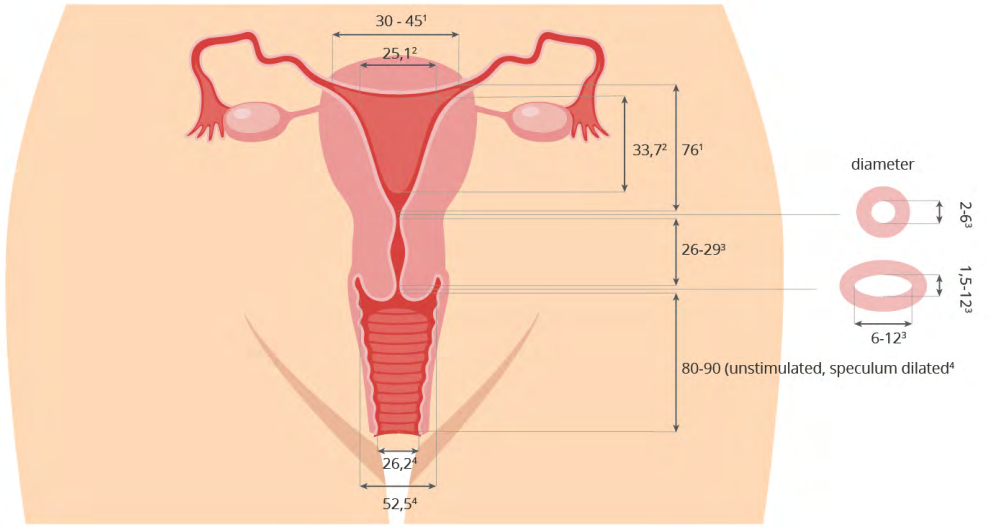


Figure 21: Antroprometric features patient based on 1 Chakravarti (2010), 2 Goldstuck (2012), 3 Harvey (2016), 4 Barnhart et al. (2006), 5 Lawrence (2004)

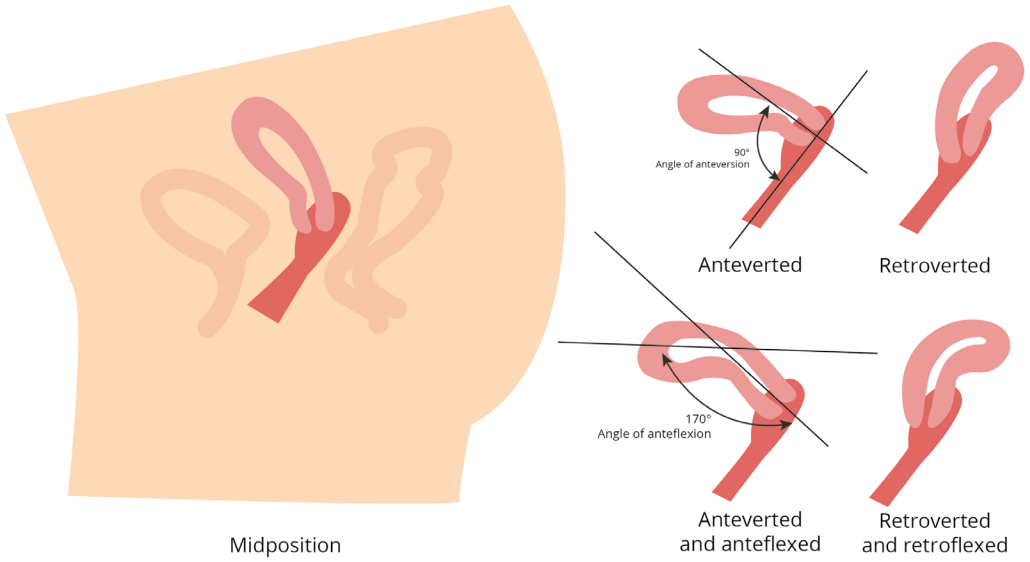


Figure 22: Orientations uteri based on Doctor lib, 2017

Finally, the Principles of Universal Design (Story, 1998) for maximising usability are used to set additional guidelines for physical ergonomics. The main guidelines that are important for optimal use of this product are:

- *"Use reasonable operating forces."*
- *"Provide adequate space for the use of assistive devices or personal assistance."*
- *"Accommodate right- or left-handed access and use."*
- *"Minimize sustained physical effort."*

Cognitive ergonomics

Cognitive ergonomics is a less tangible concept of ergonomics, but still very important to keep in mind while designing a product. The goal is to make the product intuitive to use by the gynaecologist. The guidelines that will be used for the design of it are based on the Principles of Universal Design (Story, 1998) for maximising usability. The main guidelines that are important for the intuitiveness of this product are:

- *"Arrange information consistent with its importance."*
- *"Provide effective prompting and feedback during and after task completion."*
- *"Provide adequate contrast between essential information and its surroundings."*
- *"Arrange elements to minimize hazards and errors: most used elements, most accessible; hazardous elements eliminated, isolated, or shielded."*

Conclusion

The user is analysed to understand the needs of the gynaecologist and the patient. The ergonomic needs and the journey of the patient at the gynaecology department are the basis for the requirements in the text box. These derived requirements are added to the requirements from the medical and product analysis. The next section links the user and the product in a system.

Derived requirements:

- The product needs to fit the anthropometric dimensions of the gynaecologists: female + male 25-65 years old.
- The product needs to fit the anthropometric dimensions of the female reproductive organs of the patient: female 20-50 years old.
- The product must be able to be used by a gynaecologist for a maximum of 10 minutes without experiencing discomfort.
- The product must provide adequate space for the use of assistive devices or personal assistance.
- The product must be able to be used by right- and left-handed gynaecologists.
- The product must avoid the need for sustained physical effort.

2.4 System analysis

Introduction
The system analysis links the product to the users. Besides the gynaecologist and the patient, other stakeholders and their interests are discussed. The product will be evaluated to which medical class it belongs. Research illustrates what the costs of fertility research and ART are. It shows how much the product could potentially save the health insurance. In the next section, the concluding design brief will be set up with the main conclusions of the analysis phase.

Stakeholders
The main stakeholders that have interest in the product are mapped in the Stakeholder Map in Figure 23. A short description and their supposed main interest are further explained in Appendix 10.

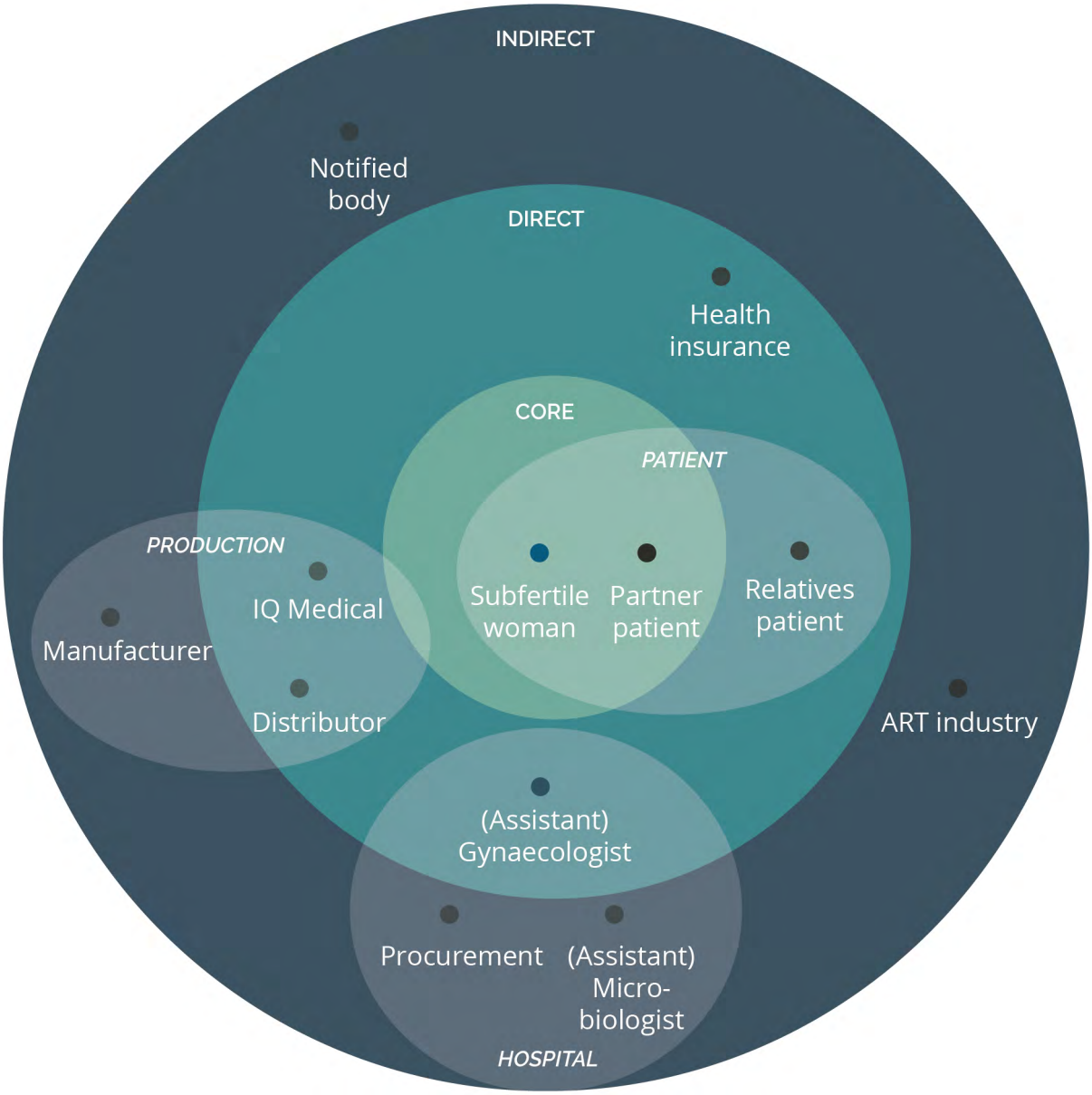


Figure 23: Stakeholders

Medical classification

The product is a medical device and has a class according to a classification system of the Medical Device Regulations (MDR) (Official Journal of the European Union, 2017). Figure 24 shows an overview of the medical device classes. The product belongs to 'Class 1s' because of the following:

- The product is invasive through an internal body orifice and has contact with mucosa.
- The duration of use is a maximum of 10 minutes, and therefore the product is intended for transient use (usage less than 60 minutes).
- The product is for a non-surgical purpose.
- The product needs to be sterile.

Currently, the Medical Device Directive is still valid, but there is now a transition period towards the MDR that is valid from 2020 (European Commission, 2018). According to the Medical Device Directive, a notified body is only needed for a class 1 device when it needs to be sterile. In the MDR a product in class 1 always needs to have a notified body. The product must be made out of biocompatible material approved by Conformité Européenne (CE) for medical products.

IQ Medical Ventures has been assessed with the conformity assessment procedure described in Article 11.3.a and Annex II excluding section 4 (Module H2) of Council Directive 93/42/EEC on Medical Devices for another product. This is sufficient for the Class 1s of the product (Medical Devices CE marking & European Authorized Representative service, 2018).

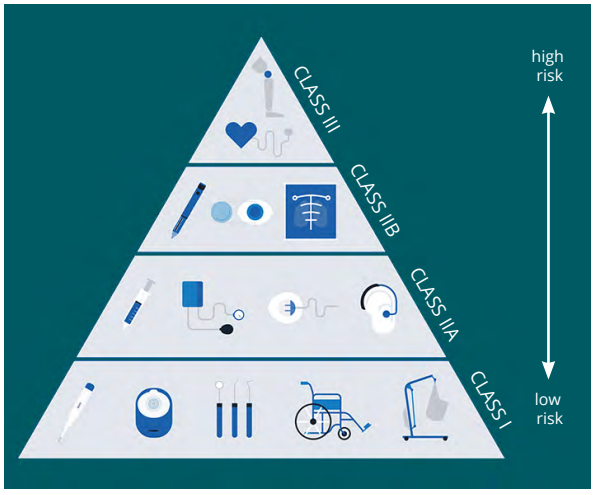


Figure 24: Medical device classes (based on Laegemiddel Styrelsen, 2016)

Price analysis

In the price analysis, the costs of fertility research and the sales prices of similar products are analysed. It indicates how much the product might save the health insurance and what the sales price of the product could be.

The average costs of a successful IVF or intracytoplasmic sperm injection (ICSI) were in 2004 €10.250 (Radboud UMC, 2010). The average costs per cycle including medicine was €2.500 of which the rate of success per cycle was 24%. After a year 45% of the treated woman became pregnant. In the Netherlands, the first three IVF/ICSI treatments will be reimbursed via the basic health insurance till the age of 42 (Freya, n.d.). Figure 25 shows an overview of the costs of fertility research and ART, based on a price chart of the UMC Utrecht in 2017. The maximum costs of fertility research can be even higher according to Prof. Dr. Mark Hans Emanuel (personal communication, October 12, 2018), depending on the different types of research or surgery. If the product that examines the uterine microbiome could exclude the need for extensive fertility research or could increase the rate of success of an IVF cycle, it could make considerable savings.

Figure 26 lists the costs of the three similar procedures of Figure 13. Often these tests are extra and are not reimbursed by health insurances. Therefore these costs are usually paid by the couple. If research proves its cost-effectiveness, it is likely health insurances will start to reimburse the costs. If the costs of the uterine microbiome sampler are below its proven potential savings, health insurances might reimburse the costs.

This analysis shows the sales prices of some competitors. It indicates how much the uterine microbiome sampler can cost. According to IQ Medical Ventures (personal communication, October 03, 2018), the production costs should be lower than 30% of the sales price to be profitable.

Conclusion

The text box summarises the conclusion of the system analysis in the essential requirements. The requirements focus mainly on safety and costs. These requirements need to be kept in mind to allow the product to enter the market. The requirements are added to the requirements from the medical, product and user analysis. The next section will conclude the analysis.

Derived requirements:

- The product must conform to the MDR.
- The product must be designed to minimise hazards.
- The product needs to be designed and produced conforming to the MDR.
- The product needs to be produced in a sterile surrounding.
- The product must be made out of biocompatible material approved by CE for medical products.
- The product needs to be packaged conforming to the MDR.
- The sales price of the product needs to be slightly lower than direct competitors: below €800,-.
- The production costs need to be lower than 30% of the sales price.

Type of costs	Minimum costs	Maximum costs
Fertility research man	€ 269,57	€ 641,69
Fertility research woman	€ 330,04	€ 2.264,03
Fertility research couple	€ 599,61	€ 2.905,72
Transplantation cycle IVF	€ 2.228,19	€ 3.428,19
Transplantation cycle ICSI	€ 2.531,19	€ 3.731,19
Tranplantation costs IVF/ICSI 1-3 cycles	€ 2.228,19	€ 11.193,57
Fertility research costs per pregnancy per couple	€ 599,61	€ 2.905,72
Transplantation costs per pregnancy	€ 2.228,19	€ 11.193,57
Total costs per pregnancy	€ 3.130,80	€ 3.130,80

Figure 25: Costs fertility research and ART (UMC Utrecht, 2017)

Similar product	Minimum price	Maximum price
ERA: Intrauterine test, NGS (personal communication, September 17, 2018)	€ 800,00	€ 1200,00
ReceptIVFity: Vaginal swap, NGS (ReceptIVFity, 2018)	€ 363,00	-
Fertilome: Blood test & advice (Fertilome, 2018)	€ 850,92	-

Figure 26: Costs similar products

2.5 Concluding design brief

Introduction
The analyses of the previous sections are the basis of a concluding design brief. An infographic summary shows the most important insights and the main requirements are listed. These requirements are used to assess the ideas in the next phase. The Problem Definition, design goal and the Design Vision are made up for the creation of the product in the next phase.

Infographic summary
In the analysis, several reasons for the existence of this product are mentioned and in the infographic of Figure 27 the main facts and figures for this are summarised.

Relevance of project
There are multiple reasons why this device is relevant for the patient in its context. If there is a link between the uterine microbiome and subfertility, there are various reasons why it is beneficial to have a device that can take this sample. The possible value of this product could be:
- Increase the success rate of natural pregnancy
- Increase the success rate of ART and decrease the number of cycles IVF/ICSI needed
- Better inform the patient about a possible cause of subfertility
- The couple can save money by requiring less expensive ART procedures
- Health insurance can save money by requiring to reimburse less expensive ART procedures

Requirements and preferences
The Programme of Requirements is based on the requirements that derived from the total analysis. Appendix 11 shows the complete Programme of Requirements. In consultation with IQ Medical Ventures and gynaecologists, several main requirements and main preferences are listed. The main requirements will be used to assess the ideas in the creation phase. These requirements are focussed on securing a non-contaminated sample, ensure patient safety and its patentability for IQ Medical Ventures. Several main preferences will be used to assess the concepts and to improve the design of the chosen concept. These preferences are focused on evaluating its error sensitivity, the ease of handling, the production costs, the patient comfort and a link between a research and commercial version of the product.

Main Requirements

Non-contamination:
- The product must be able to take a non-contaminated transcervical sample of the microbiome of the uterine cavity.
- The product must prevent contamination with the cervix, vagina or any other part during preparing, inserting, sampling, pulling out and releasing in a test tube.
- The product needs to be able to release the sample into a test tube of the hospital for further research.

Patient safety
- The product must conform to the MDR.
- The product must be designed to minimise hazards.
- The product needs to fit the anthropometric dimensions of the female reproductive organs of the patient: female 20-50 years old.

Patentable
- The product needs to be able to be patented by IQ Medical.

Main Preferences

Error sensitivity
- *The product should be designed to minimise errors.*

Ease of handling
- *The product should be understandable with a short introduction description.*

Production costs
- *The production costs should be as low as possible.*

Patient comfort
- *The product should preferably have a maximum diameter of 4mm.*
- *The product without handle should preferably have a length of minimum 225 mm.*
- *The product procedure should be as comfortable as possible for the patient.*

Link research & commercial
- *The product should be able to be produced as a research version for scientific research.*

Figure 27: Infographic summary

Problem definition
The Problem Definition of the thesis is concluded based on research. It describes the current state and the need for the development of the product. The Problem Definition is focused on subfertility and can be extended when research shows more about the link between the uterine microbiota and other gynaecological disorders. Appendix 12 shows a framework in which research, industry and the hospital are linked in the development of a product like the uterine microbiome sampler. Each of them has different stakes in such a product.

Design goal
The Design goal is the aimed deliverable of this graduation. By designing a sampler that can take a non-contaminated sample, it will suit the described problem in the Problem Definition. The sampler will be created and tested to evaluate if it genuinely meets the goal.

Design vision
The Design Vision Statement describes the declaration of the design objective, intended to guide the decision-making process. This vision is linked to the main preferences and will be used to improve the design of the chosen concept.

Conclusion
In the concluding design brief, the important takeaways are concluded. This concluding design brief will be the basis for creating the concept and will be used during testing to reflect on whether the product fulfils the requirements and preferences. In the final phase, the design goal will be reflected upon.

Problem Definition:
There is currently no medical device for taking a non-contaminated sample of the uterine cavity to examine the microbiome. This hinders research concerning the relation of the uterine microbiome and (sub)fertility.

Design Goal:
Design a sampler for taking a sample of the uterine cavity without contamination for research concerning the relation of the uterine microbiome and (sub)fertility.

Design Vision Statement:
The sampler should be able to take non-contaminated material of the uterine cavity to examine the microbiome, while having the highest usability for the gynaecologist, being the most patient-friendly and being suitable to sample material for modern microbiological research methods like Next-Generation Sequencing.

3. CREATION

The creation of the concept is the focus of this phase. The ideation process results in concept ideas, which are evaluated using the Programme of Requirements. Subsequently, the concepts are explained and tested. The phase ends with a concept that fits the most with the Programme of Requirements. The final concept developed in the creation phase will then be elaborated on further and tested in the next phase.

3.1 Pre-concept

Introduction
This section explains the creation of the concepts. Ideas were generated in creative sessions and during observation and co-creation at the UMC Utrecht. These ideas contributed to four concept ideas. The concept ideas were assessed on the main requirements, which derived from the analysis. This assessment resulted in two concepts that will be further developed in the next section.

Creative sessions
Multiple creative sessions were organised at Delft University of Technology and IQ Medical Ventures, Figure 28. During these sessions, several Distant Analogies of similar situations were used for first inspiration. Subsequently, the participants generated ideas with How-To's: how to enter the uterus, how to take a sample, how to exit the uterus, how to place the sample in a test tube and how to prevent contamination during these actions. The participants used Brainwriting and Brain Drawing to generate ideas. At the end, the participants combined several partial solutions towards a total product solution.

Observation & co-creation @ UMC Utrecht
At the UMC Utrecht, additional observations took place at hysteroscopic surgeries (Appendix 5). These observations demonstrated the difficulties involved with taking a non-contaminated sample. They also provided a better understanding of the anatomical differences of patients and handling of different gynaecological instruments. Afterwards, several ideas and concept directions were discussed, evaluated and elaborated on with the gynaecologist and gynaecologists under training.

Figure 28: Creative session at TU Delft

Concept idea generation

To generate concept ideas, partial solutions for several functions of the product were generated. Figure 29 summarises the most promising partial solutions in a Morphological Chart. The explanation of why these functions in particular were chosen as the most essential is presented in Appendix 13.

Appendix 14 shows the combination of partial solutions into seven concept ideas. These concept ideas are discussed, evaluated and elaborated on with a gynaecologist, a midwife and gynaecologists under training. The four most promising concept ideas are shown with the lines in the morphological chart in Figure 29.

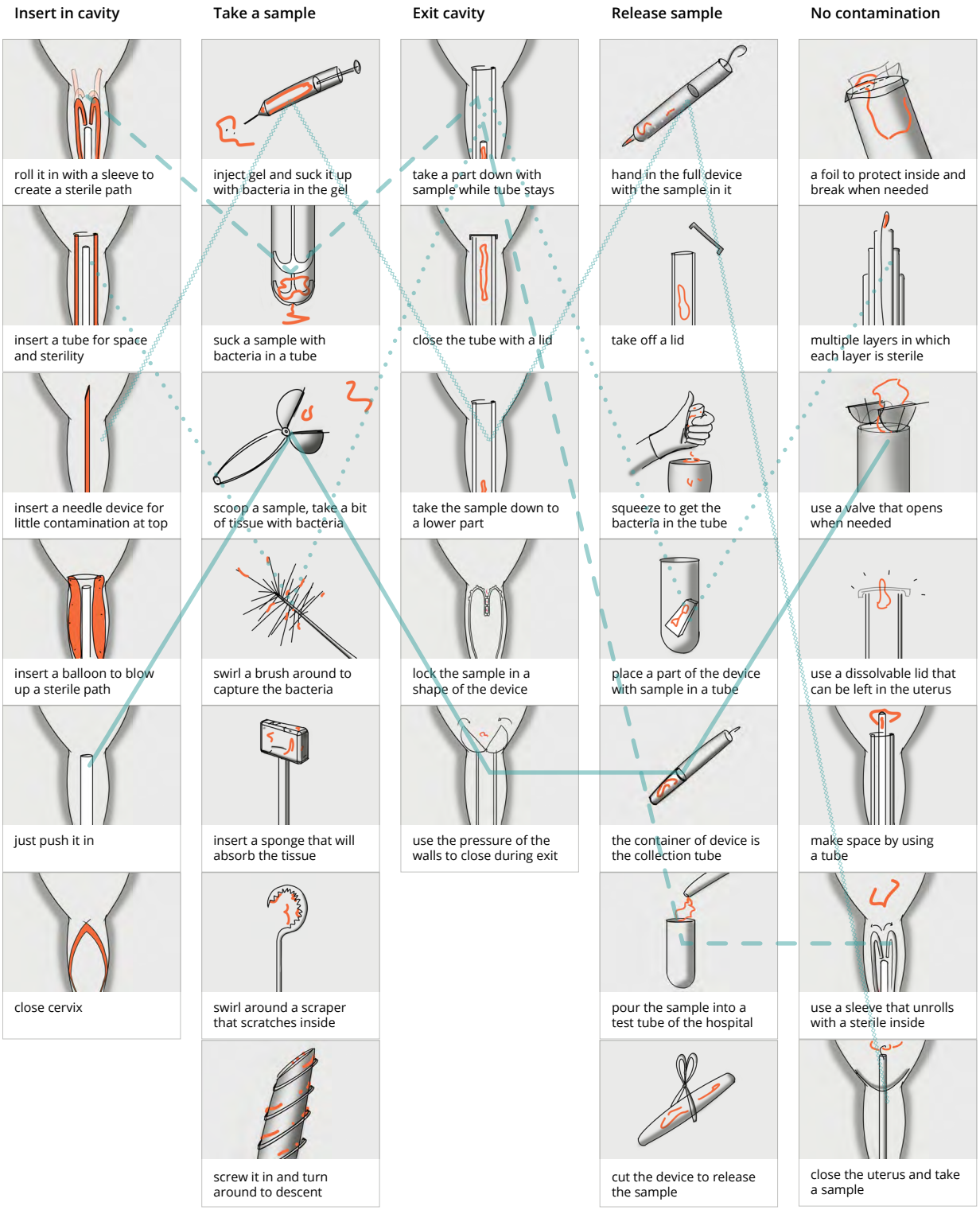


Figure 29: Morphological Chart

Each of the concept ideas will be assessed by the main requirements of the product to evaluate if they comply. Figure 30 shows the concept ideas. First, the general idea of all four concept ideas is briefly explained.

The concept idea Gel Infusion is based on a product that IQ Medical already has already developed for other applications, the ExEm Foam kit. By closing the uterus with a plug, a gel can be injected. The bacteria would mix with the gel and then be removed from the uterus directly using the syringe.

The concept idea Protective Tongs is based on a tea egg. By delivering a closed product into the uterus, the inside will stay protected. By pushing on the bottom of the device, the half spheres will open, and the sampler will extend toward the top. On the way back the sphere will close back again, and the sample is protected.

Concept ideas

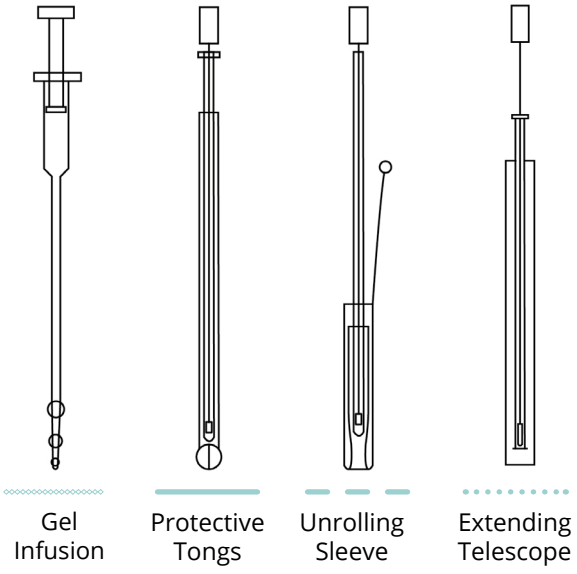


Figure 30: Concept ideas

The concept idea Unrolling Sleeve is based on a sleeve that is rolled inwards, and while pushing with the sampler from the inside, the sleeve will unroll. While unrolling, every time a new clean, sterile part will come forward. After taking a sample, the device should be pulled back before the sleeve will be removed.

The concept idea Extending Telescope is based on a telescope. The product has different tubes inside each other and is protected by silicon valves. By pushing the inner tube upwards, the protection valve will open, and a new, sterile tube appears. A brush is protected by two of those layers. The sampler needs to be pulled back before the tubes are pulled back, to prevent contamination.

Main Requirements

Non-contamination:

- The product must be able to take a non-contaminated transcervical sample of the microbiome of the uterine cavity.
- The product must prevent contamination with the cervix, vagina or any other part during preparing, inserting, sampling, pulling out and releasing in a test tube.
- The product needs to be able to release the sample into a test tube of the hospital for further research.

Patient safety

- The product must conform to the MDR.
- The product must be designed to minimise hazards.
- The product needs to fit the anthropometric dimensions of the female reproductive organs of the patient: female 20-50 years old.

Patentable

- The product needs to be able to be patented by IQ Medical.

Concept idea assessment

The concept ideas that will be further developed need to fulfil the most important requirements. Therefore, the concept ideas were rated according to the main requirements to make a differentiation in inspirational ideas and promising concepts. The concept ideas were rated in expert consults with IQ Medical Ventures and gynaecologists with a Radar Chart Assessment, Figure 31. The green area shows the minimum score to which the concept ideas need to comply with to be further developed as concepts.

As can be seen in the Radar chart, two of the four initial concept ideas did not meet the requirements. The concept idea Protective Tongs has been discarded because there were some doubts on the patient's safety. The concept idea Gel Infusion raised several questions about whether it would be able to prevent contamination. Appendix 13 presents the experts' opinion on all the concept ideas. This assessment resulted in the continued development of the concept ideas Unrolling Sleeve and Extending Telescope, Figure 32.

Conclusion

The ideation resulted in several concept ideas. These concept ideas were tested against the main requirements. Two concept ideas met the requirements and will be further detailed in the next section.

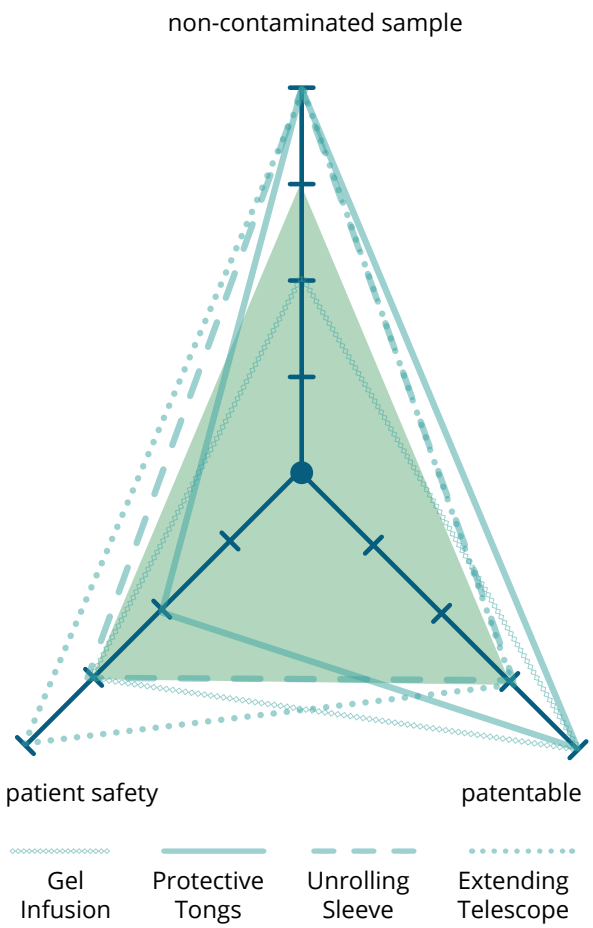


Figure 31: Radar Chart Selection on requirements

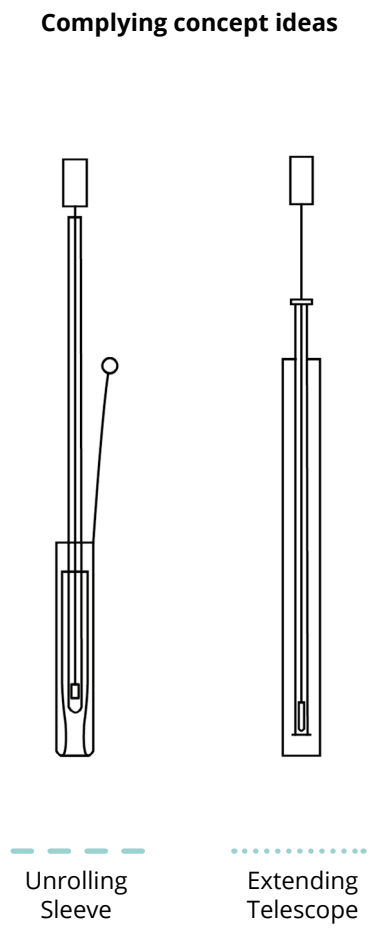


Figure 32: Concepts ideas conform requirements

3.2 Concepts

Introduction
This section illustrates the two concepts in more detail. It explains the functioning of the concepts Unrolling Sleeve and Extending Telescope. More information about the concepts is shown in Appendix 15. In the next section, both concepts are prototyped to evaluate if the concepts are functioning as intended and comply to the main preferences.

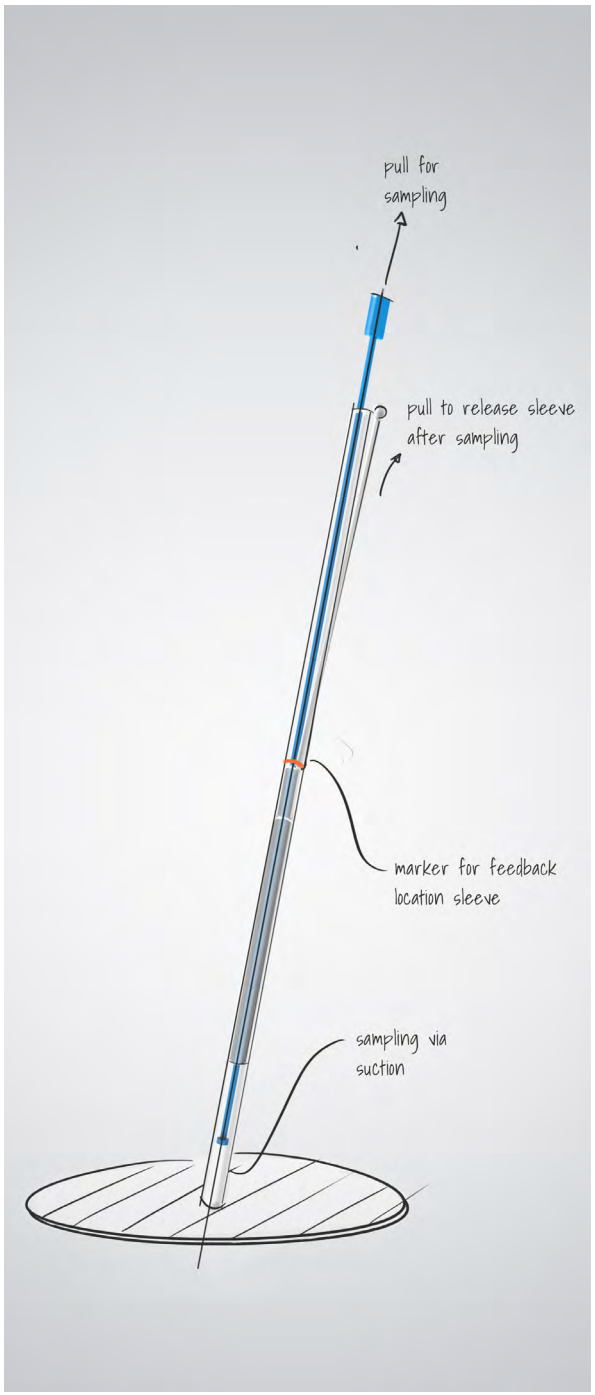


Figure 33: Concept Unrolling Sleeve total

Concept 1: Unrolling Sleeve
The concept Unrolling Sleeve is a sampler based on suction with an inwardly rolled sleeve around it, Figure 33 and Figure 34. This sleeve prevents contamination while the sampler is inserted in the cervix. A scenario of the different steps of the product is presented in Figure 35. While inserting the sampler, the sleeve unrolls and every time a new sterile part of the sleeve will be in front. After reaching the internal ostium, the sampler can be pushed forward until the sleeve reaches a marker which shows the sampler is not protected by the sleeve anymore. From this moment, the piston of the sampler can be pulled back to create a depression in the tip of the sampler. The sample will be sucked into the tip. After sampling, the sampler will be released through the sleeve and inserted in a test tube for research. Then the sleeve can be released via a pulling cord.

The sleeve will improve the patient's comfort by its ease of sliding in. A research version can be made by using commercially available samplers, for example, the Pipelle. For this research version, only the sleeve needs to be designed.

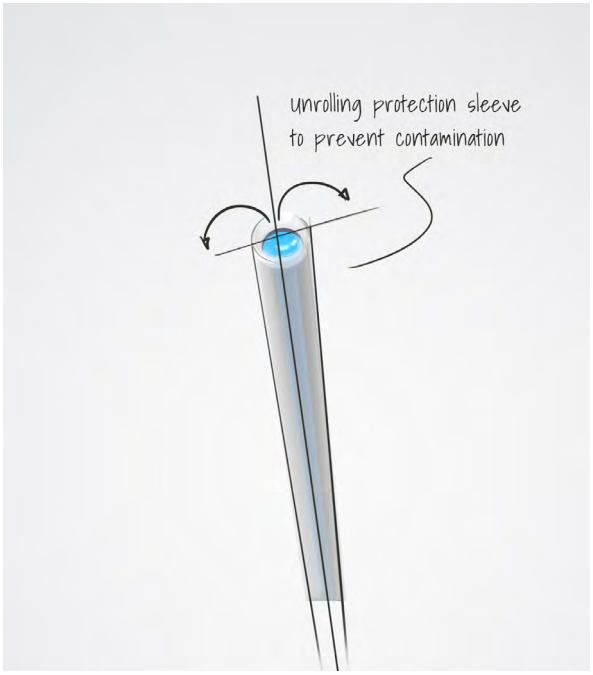
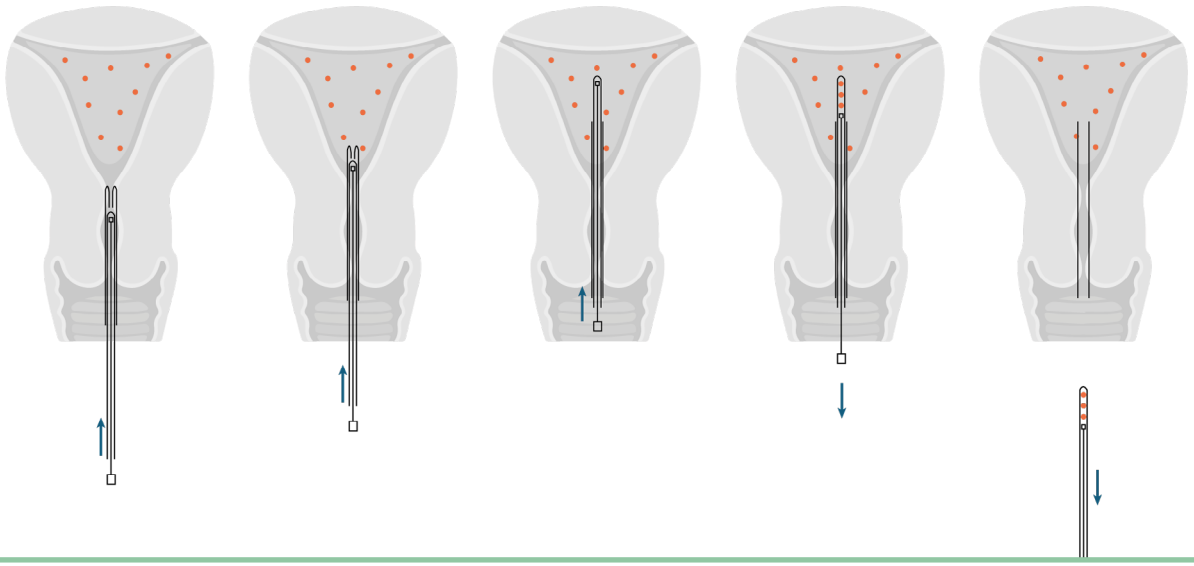


Figure 34: Concept Unrolling Sleeve tip

Scenario of taking a sample

1.	2.	3.	4.	5.
insert device and unroll sleeve	insert and unroll until after internal ostium	push sampler further in the uterus	take sample by pulling at the suction handle	retract sampler ready for further research

Overview of taking a sample



Zoom in on tip

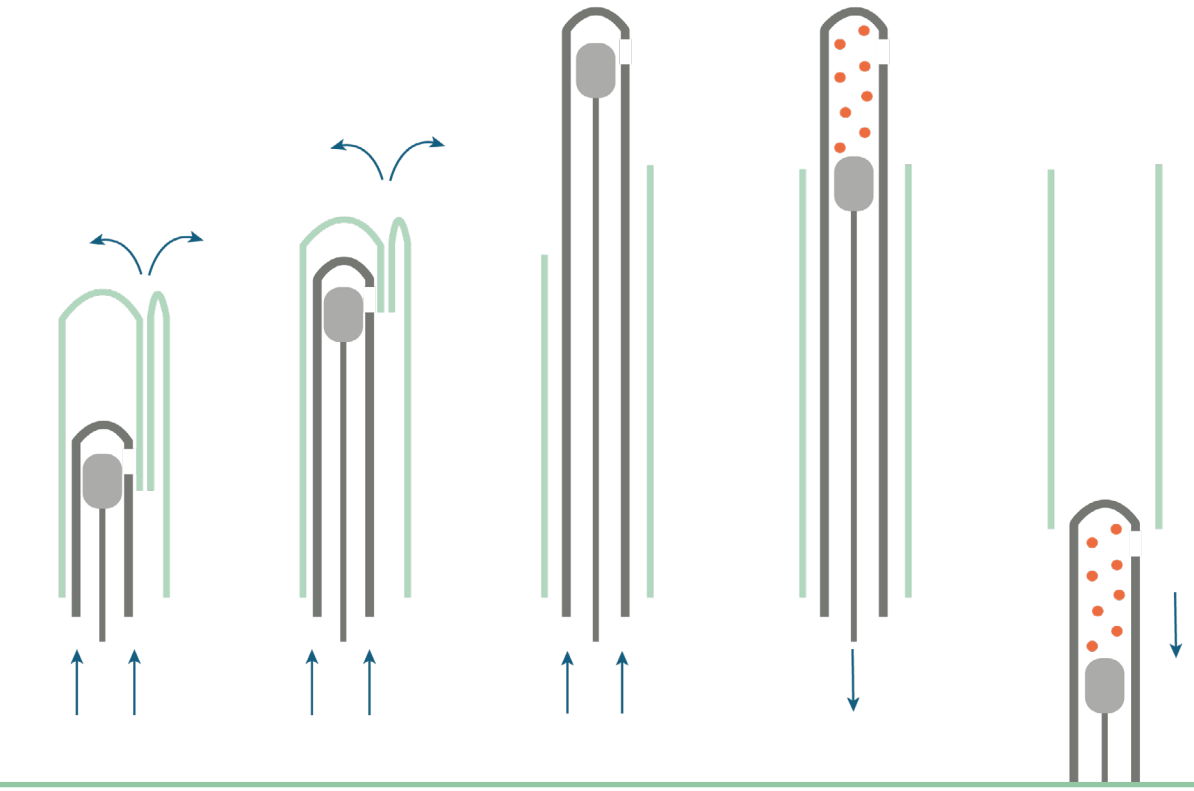


Figure 35: Scenario concept Unrolling Sleeve

Concept 2: Extending Telescope

The concept Extending Telescope is a layered product that extends in the uterus of the patient, Figure 36 and Figure 37. A brush sampler is protected by two tubes, and each tube is protected with film layers for contamination prevention. A scenario of the different steps of the product is presented in Figure 38. When the device is inserted in the uterus, right after passing the internal ostium, the inner tube will be pushed forward to break the foil of the outer tube. Directly after, the handle of the brush will be pushed forward to break the foil on the tip of the inner tube. By turning the handle, the sample will be taken with the brush. After sampling, the brush will be pulled back into the inner tube and released from the body of the patient. The sample from the brush will be released in a test tube, and finally, the inner and outer tube will be released from the patient.

The concept Extending Telescope makes sure the gynaecologist has control over the moment that the product will be opened and the location where the sample will be taken. By taking a sample with a brush or swab, the sampling procedure will be less painful for the patient (Cook Medical, 2018).

Conclusion

This section presented the design of both concepts in further detail. In the next section, the concepts are both prototyped. A functional test will show if the concepts perform as intended. In this test, the concepts will be evaluated on the main preferences from the analysis phase.

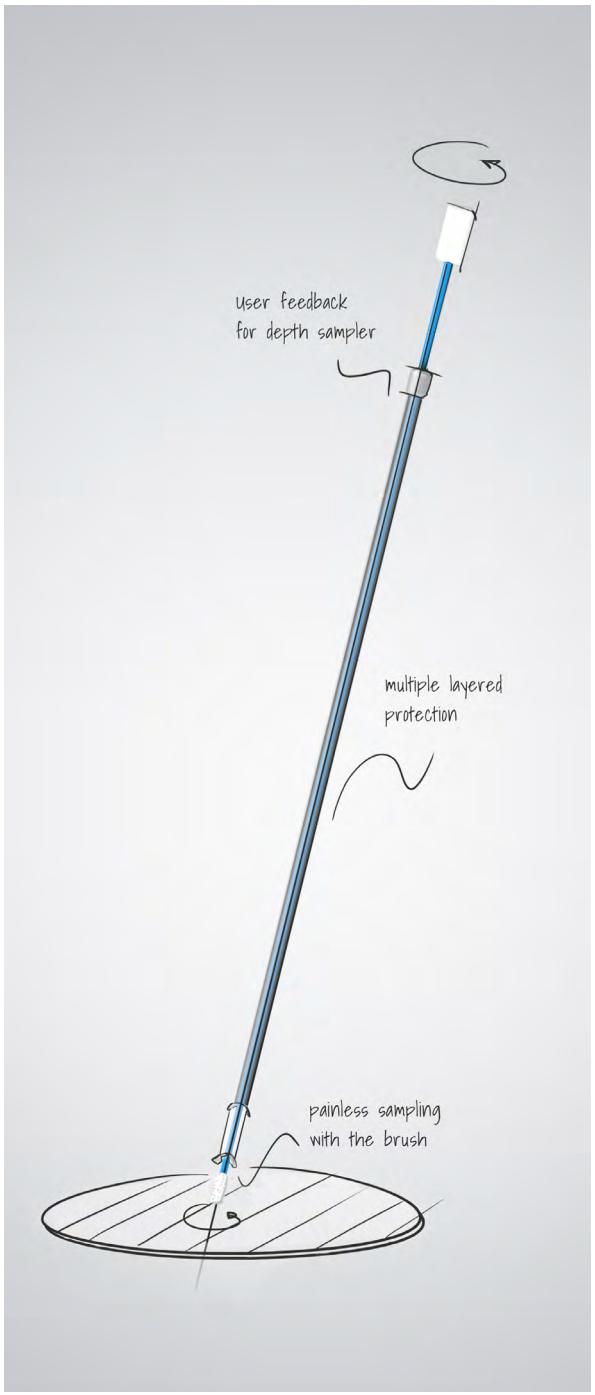


Figure 36: Concept Extending Telescope total

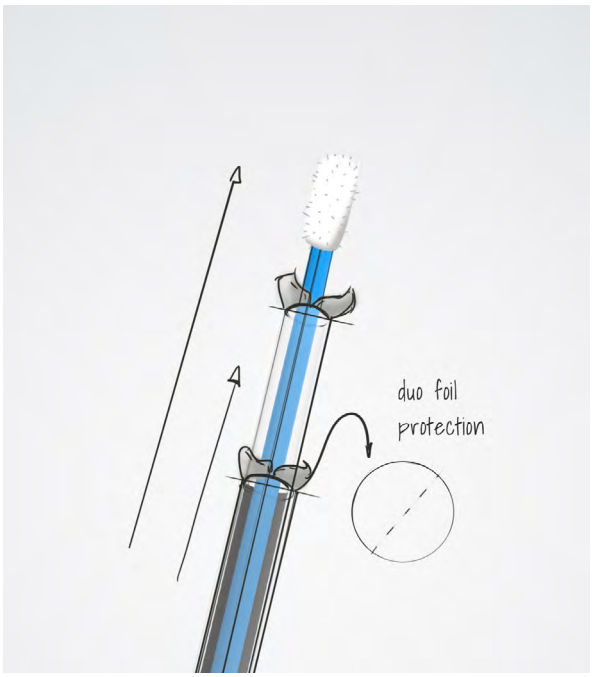
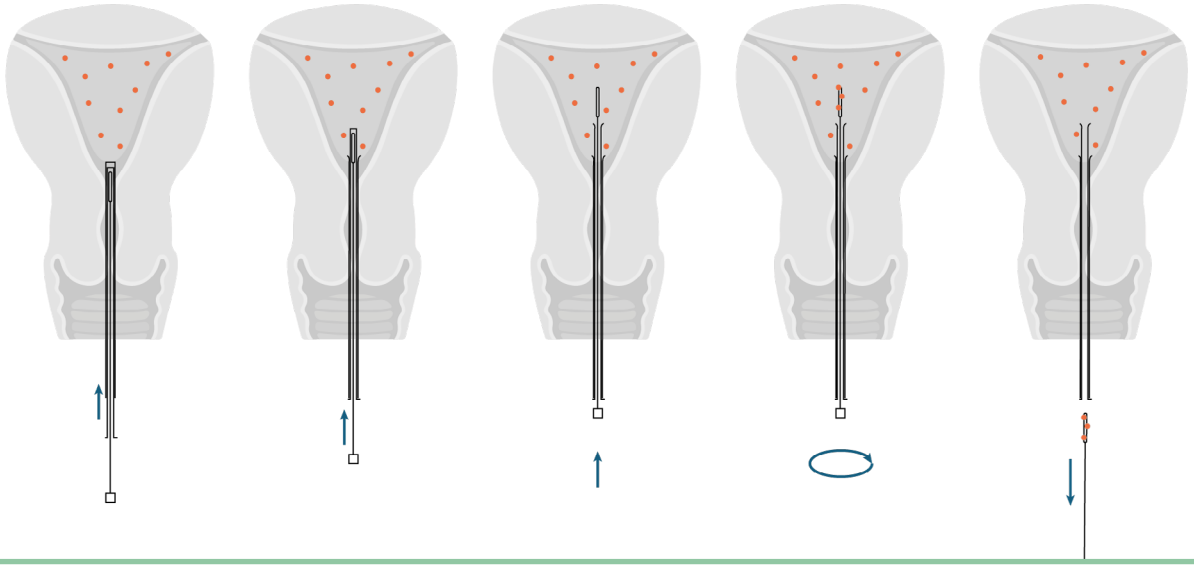


Figure 37: Concept Extending Telescope tip

Scenario of taking a sample

1.	2.	3.	4.	5.
insert until after internal ostium	push inner tube through outer tube, open valve	push swab through inner tube, open inner valve	turn swab to take a sample	retract swab ready for further research

Overview of taking a sample



Zoom in on tip

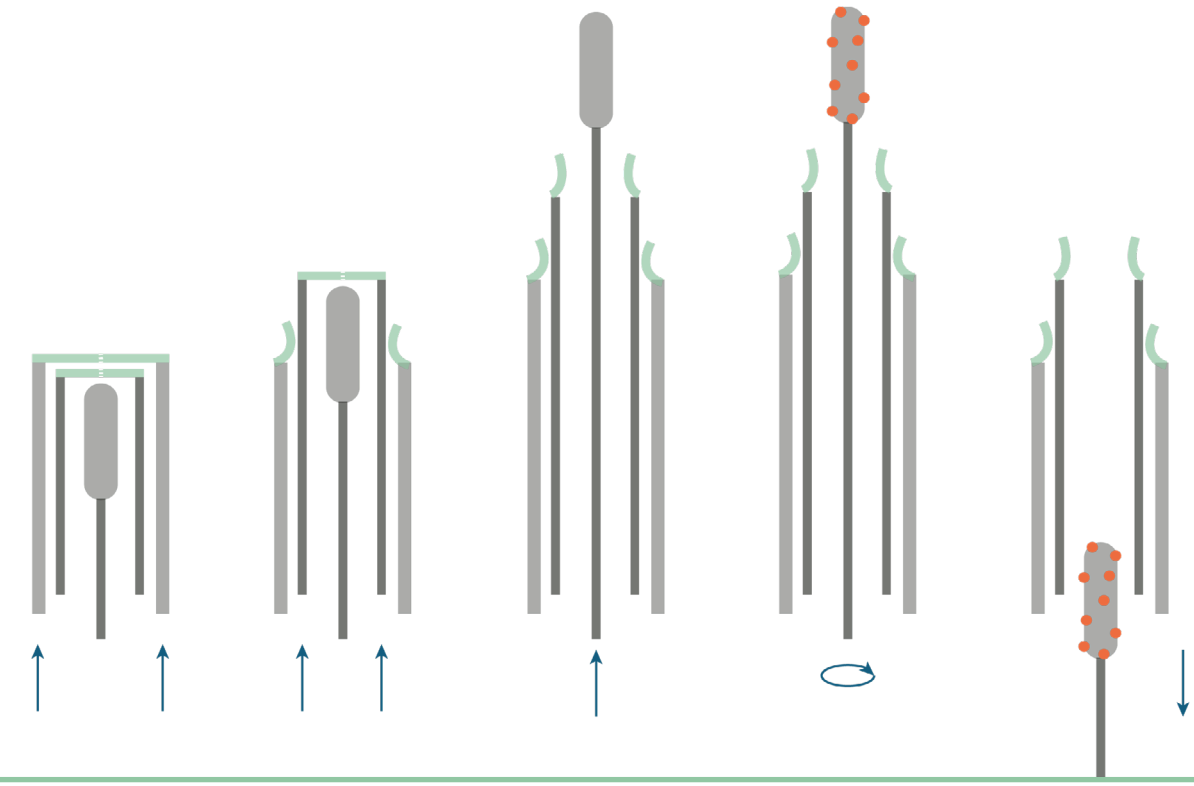


Figure 38: Scenario concept Extending Telescope

3.3 Concept test

Introduction
The concept test shows how the concepts function in a 3D environment. By Three-Dimensional Modelling, the concepts could be tested in a Feasibility Study. Based on this test, the concepts could be assessed with a Harris Profile on five important preferences of the project.

Test set up
The test set up consisted of several parts. Two 'uteri' of the patient were made out of a plastic tray with foam walls, representing the walls of the cervix. The 'bacteria of the uterus' were made out of hair gel, while the 'bacteria of the cervix' were represented by apple syrup. These viscose materials were chosen to show the flow of the 'bacteria'. A 5:1 prototype was built for both concepts to be able to execute the test. During the test, the sampler was inserted int he uterus, a sample was taken and the sampler was retracted. Appendix 16 explains more about the test set up.

Results
Figure 39 and Figure 40 show the samplers in the uteri. Both of the concepts could take a sample without visible contamination, Figure 41 and Figure 42. The test results did not show whether the concepts were non-contaminated on a more detailed level. The full execution process is presented in Appendix 16.

Conclusion
Both of the concepts fulfil the main functionality and can take a sample without visible contamination. In the next section, the concepts will be assessed on the main preferences that derived from the analysis to decide which concept is most promising.

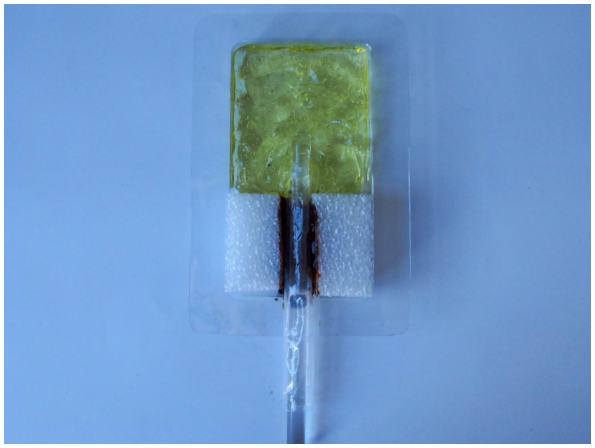


Figure 39: Unrolling Sleeve in uterus

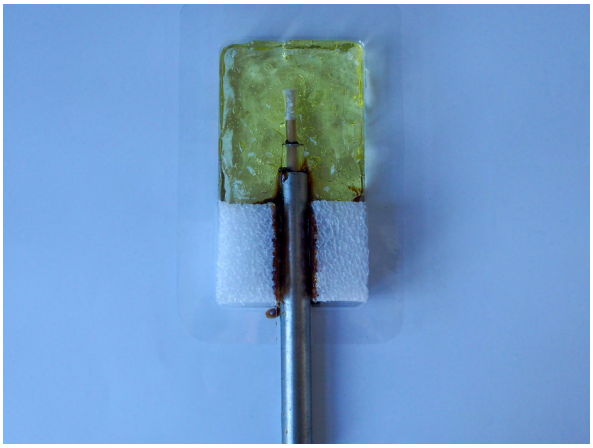


Figure 40: Extending Telescope in uterus

Figure 41: Unrolling Sleeve sample

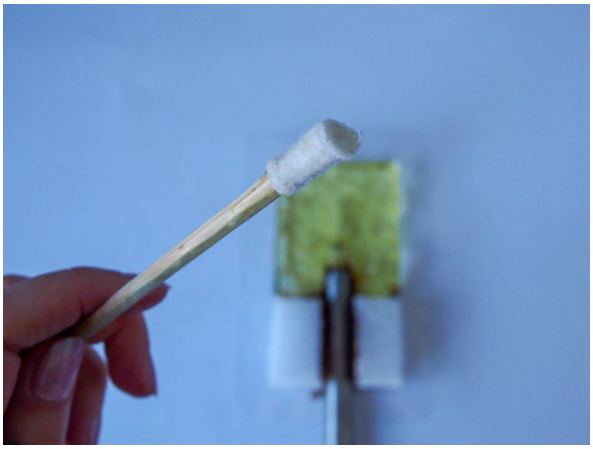


Figure 42: Extending Telescope sample

3.4 Concept assessment

Introduction
The test evaluated several aspects of the concepts that could only be assessed using the physical prototypes. A Harris Profile evaluated the concepts on five important preferences from the List of Requirements. This assessment resulted in the continuation of one concept, which will be further prototyped and tested in the next phase.

Error sensitivity
The error sensitivity is of importance to make sure the device is as foolproof as possible. The preferences of error sensitivity and the ease of handling are linked. If the concept is easy to handle, it is less likely errors will occur. Still, a concept can be hard to handle, but no errors will occur. For example, the Unrolling Sleeve was hard to unroll, but this did not necessarily result in contamination. On the one hand, it was possible to take a sample of the inside of the sleeve when it was not unrolled properly. On the other hand, it was possible that the sleeve was already retracted too far before reaching the internal ostium, which would result in contamination. In the test, the location of the sampler and the position of the sleeve were visible. However, when the sampler is used inside the uterus the position would not be visible. The Extending Telescope was surprisingly easy to operate which made it easy to prevent errors. Each of the steps made sure it was possible to take a sample at the right spot while protecting it onwards.

Ease of handling
The ease of handling is of importance to make sure the gynaecologist can take a non-contaminated sample intuitively. The Unrolling Sleeve often needed two hands to make sure it was unrolling well. In this test, the operator was able to see the tip of the sampler and could adapt to it. Inside the uterus, the operator is not able to see how the sampler is acting. The Extending Telescope requires two steps, but it was functioning quite instinctively. With one hand you could hold the product while the other hand was able to extend an inner layer.

Production costs
The production costs are of importance for the ability to make a profit on the product. The Unrolling Sleeve is likely to be a little more expensive because it requires a specific material and a more specific assembly. These expenses can be reduced when an existing sampler is used in the concept. The Extending Telescope has more parts, but these parts probably require less specialist production.

Patient comfort
Patient comfort is of importance to make sure the patient is experiencing the least pain. For the research version, the Unrolling Sleeve has a smaller diameter. The Extending Telescope requires two tubes and a brush. Therefore, it can be thicker than the Unrolling Sleeve and cause more discomfort.

Link research and commercial
The link of a research and commercial version is of importance to make sure the research version proves that a commercial version of the product would function well. Otherwise, a whole new design and proof of functioning are needed. The research versions of the concepts can both use existing samplers or parts. For the commercial versions, a whole integrated design could be made.

Main Preferences

Error sensitivity
- *The product should be designed to minimise errors.*

Ease of handling
- *The product should be understandable with a short introduction description.*

Production costs
- *The production costs should be as low as possible.*

Patient comfort
- *The product should preferably have a maximum diameter of 4mm.*
- *The product without handle should preferably have a length of minimum 225 mm.*
- *The product procedure should be as comfortable as possible for the patient.*

Link research & commercial
- *The product should be able to be produced as a research version for scientific research.*

Harris profile

The Harris Profile shows that the concept Extending Telescope has the most potential of becoming a successful product, Figure 43. This concept was less sensitive to errors, was easier to handle and is probably cheaper to produce than the Unrolling Sleeve. Before the test, it was expected the sleeve would be the most suitable solution. The test showed how prototypes could look promising on paper, but always need to be prototyped and tested to know for sure.

The Extending Telescope was the concept that scored best on the five main preferences. The concept test showed a few aspects that are of importance for further exploration in the test phase:

- The concept scored lower on patient comfort because the product is thicker than the other concept. In further detailing, the diameter of the sampler should be as small as possible.
- The valves should be completely closed to prevent contamination and be easy to open with the inner layers.
- The connection of the valves to the tubes should be further explored. A bracket could be designed for secure positioning of the valves.
- In an expert review with microbiologists is adviced that swab would be more suitable for this application than a brush.

Conclusion

In this section, the two concepts were tested to evaluate them based on the preferences of the project. A Harris profile showed that the Extending Telescope is the most promising concept. This concept will be prototyped in more detail and tested to evaluate if it is really able to take a non-contaminated sample. Points of attention for further design are the patient comfort and the valves.

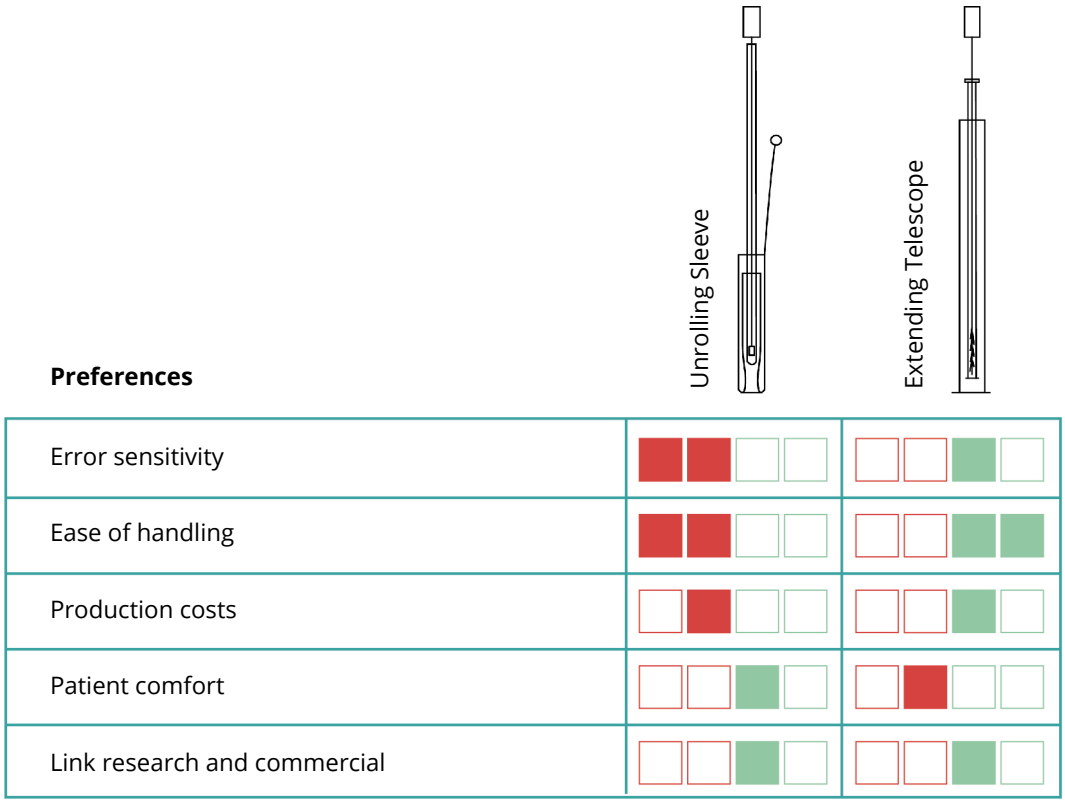


Figure 43: Harris Profile

4. TEST

A functional prototype was made and tested in vitro to evaluate if the sampler can take a non-contaminated sample. This study concludes that this sampling technique has the potential to take a non-contaminated sample. The test is evaluated in the discussion on its relevance and its limitations. Finally, recommendations were formulated on follow-up studies and the design of the sampler. These recommendations are takeaways for the last phase of this thesis and further development after the graduation.

4.1 Prior to the test

Introduction
This section shows the preparation of the microbiological test. The primary goal was to evaluate if the product can take a non-contaminated sample. Functional prototypes were made to be able to execute the test. A protocol was set up to make sure the tests were all performed in the same way. In the next section, the results of the test will be shown.

Research question
The goal of this research is to test if the designed sampling technique is able to take a non-contaminated sample. The research question is strongly linked to the design goal.

Design Goal:
Design a sampler for taking a sample of the uterine cavity without contamination for research concerning the relation of the uterine microbiome and (sub)fertility.

Research Question:
Is the designed sampling technique able to take a non-contaminated sample?

Procedure
An In Vitro Test was executed at the Medical Microbiology and Infection Control Department of the Amsterdam UMC, location VUmc, on December 21st 2018. In this test, functional prototypes were used to take a sample via a compartment contaminated with bacteria. In the results, the samples were analysed to evaluate if the designed sampling technique was able to take a non-contaminated sample. Blank tests are performed to evaluate the most important assumptions of the test.

In the procedure, the sampler was inserted through the 'cervix'. A sponge was used to mimic the cervix, and an incision was made through which the device was inserted. The grinding part of the sponge was used to represent the external ostium, having a little more resistance. The sponge was infused with a Tryptic Soy Broth (TSB) with the bacteria *Klebsiella pneumoniae* (ATCC 13883), grown for 24 hours at 37°C. *K. pneumoniae* is a common gut bacteria and is not present in the cervix. This form of bacteria was used due to its sticky consistency and the ability to easily distinguish it from the bacteria used to mimic the bacteria of the uterine cavity during the test.

A sample was taken from a sheep blood agar plate (SBA 1), to mimic sampling from the uterine cavity. Since it is not known what the concentration is of the bacteria in the uterine cavity, three different tests were performed. In the first test, the blood agar plate was sterile. In the second test, the bacteria *Enterococcus faecalis* (ATCC 29212) with a concentration of 10^2/ml was spread on a blood agar plate. In the third test, the bacteria *E. faecalis* with a concentration of 10^4/ml was spread on a blood agar plate. Low concentrations were chosen, as it is expected that the uterus has a low abundance of bacteria (Chen et al., 2017; Mitchell, 2015). After sampling, the swab was cultured in TSB for 24 hours at 37°C. If there was growth, a sterile swab from the culture medium was taken and cultured on a second sheep blood agar plate (SBA 2) to be able to reveal the bacteria. The three tests with different concentrations were all executed three times. More information about the procedure is shown in the test protocol.

The sampler can take a non-contaminated sample if *K. pneumonia* from the sponge is not present in the sample. Three assumptions are evaluated in blank tests. The first test evaluates if no *K. pneumoniae* was already present on one of the used materials. The second test shows that *K. pneumoniae* was viable. In the third test is evaluated if the procedure can take a sample of the *E. faecalis* when no *K. pneumoniae* is present on the cervix yet.

In each of the tests, the SBA 1 was checked to determine whether *K. pneumoniae* was present. If this was not the case, no contamination with the *K. pneumoniae* of the sponge had taken place when the sampler was inserted. The presence of *E. faecalis* on SBA 1 showed the concentration. In the test the presence of *K. pneumoniae* on the swab was evaluated on SBA 2. If this was not the case, no contamination with *K. pneumoniae* of the cervix had taken place during inserting and exiting the uterus. The presence of *E. faecalis* on SBA 2 showed if the swab captured the bacteria during sampling. Afterwards, the sampling procedure was evaluated to discuss the results and to formulate recommendations for the design and further testing.

Prototype

To be able to execute the test and evaluate the concept to the research question, a functional prototype was made. This iterative process of Three-Dimensional Modelling resulted in a functional prototype for an In Vitro Test. Figure 44 shows a visualisation of the prototyping iterations.

The prototype iterations helped to understand the product, its functionality and its limitations. The most important insights are listed in Figure 45.

The final prototype for the test is visible in Figure 46, a 2:1 functional prototype of the chosen concept direction. Figure 47 shows the details of the valves of this concept. The valves are clamped, glued and held together with an extra layer of cloth tape. The prototype was based on the insights of the iterative prototype process and was used to evaluate the sampling technique.

Figure 44: Prototype iterations

After the pre-test on scale 5:1, it was decided to continue with prototyping on scale 2:1. During prototyping, work adjustments were needed, because of fractions of millimetres. It showed how the scale of the prototype correlates with the challenges during prototyping.

The connection of valves to the tubes needs to withstand a large force. This connection needs to be stronger than the force required to open the valve. During prototyping, this was the main challenge and needs to be further engineered later in the process.

While prototyping a functional prototype, it is of importance to keep the research goal in mind. It is tempting to focus on other aspects as well, like visual representation or medical applicability, while this is not the goal.

During prototyping, some of the prototypes failed. Since each product is only able to be used once, prototypes cannot be tested beforehand. Possible contamination could occur because of a prototype failure instead of the inability of the sampling technique to take a non-contaminated sample.

Figure 45: Main insights resulted from prototyping

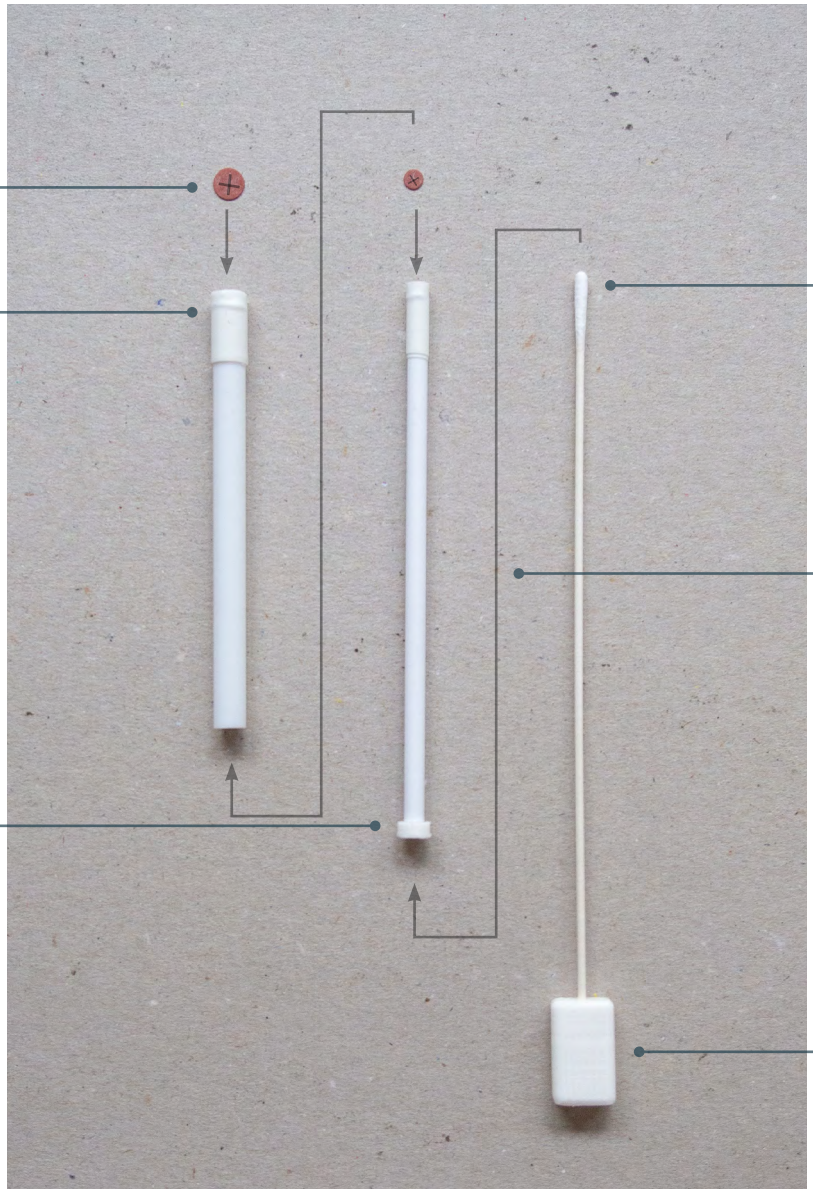


Figure 46: Functional prototype

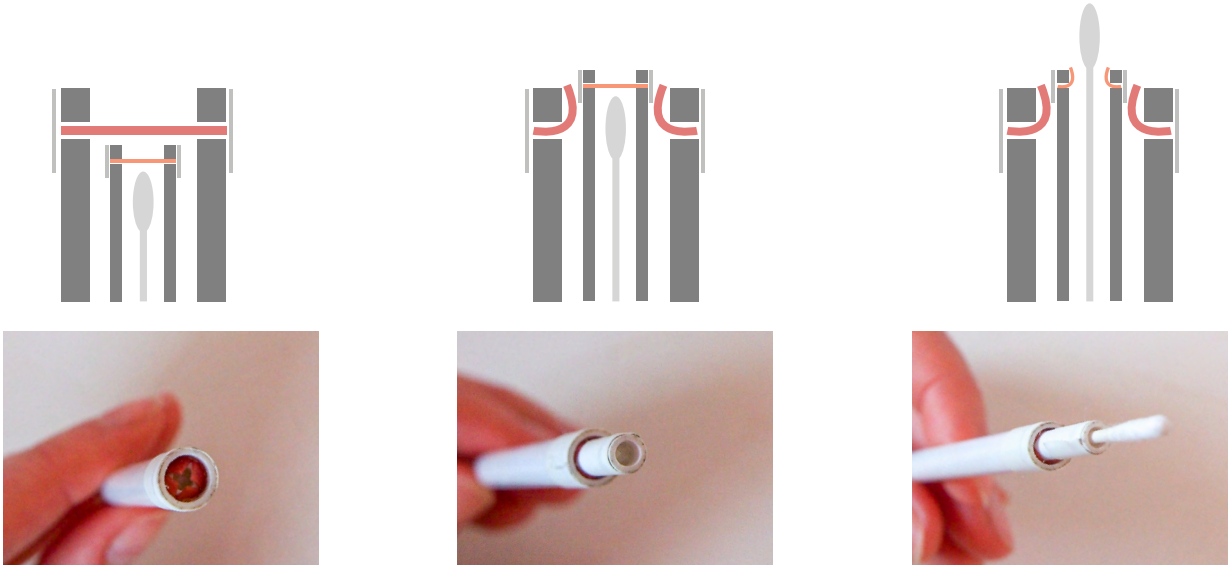


Figure 47: Details prototype

Test protocol

The test protocol was set up with the Medical Microbiology and Infection Control Department of the Amsterdam UMC, location VUmc. It is based on the procedure and applying the prototype in a test set-up.

For the test, several materials were needed, including the prototype. The main dimensions of the materials are visualised in Figure 48. The required materials needed are:

- 10 Functional prototypes scale 2:1 (Figure 49)
- 15 SBA plates
- 10 Test tubes with TSB Broth
- *K. pneumoniae* (ATCC 13883) in TSB broth
- *E. faecalis* (ATCC 29212) concentration of 10^2/ml determined via optical density
- *E. faecalis* (ATCC 29212) concentration of 10^4/ml determined via optical density
- Cleaning sponge
- Stove 37°C
- Refrigerator 4°C
- 4 pair of gloves
- Drigalski spatula
- Scissors made sterile with a Bunsen burner
- (Olympus PEN Lite E-PL6) Camera
- Pen and paper for notes

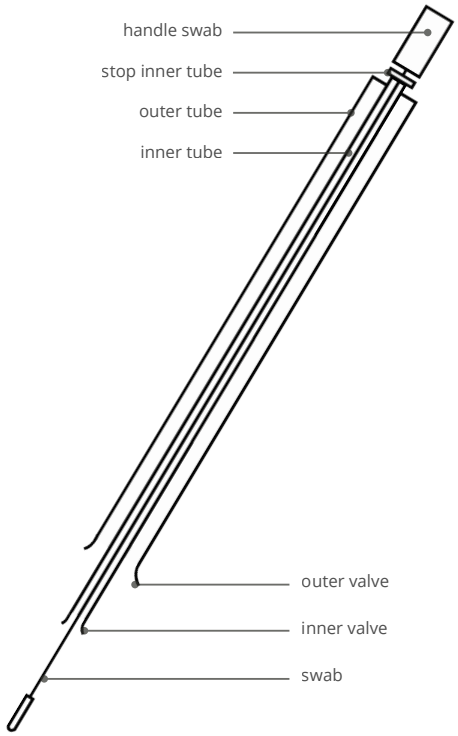


Figure 49: Parts of designed sampler

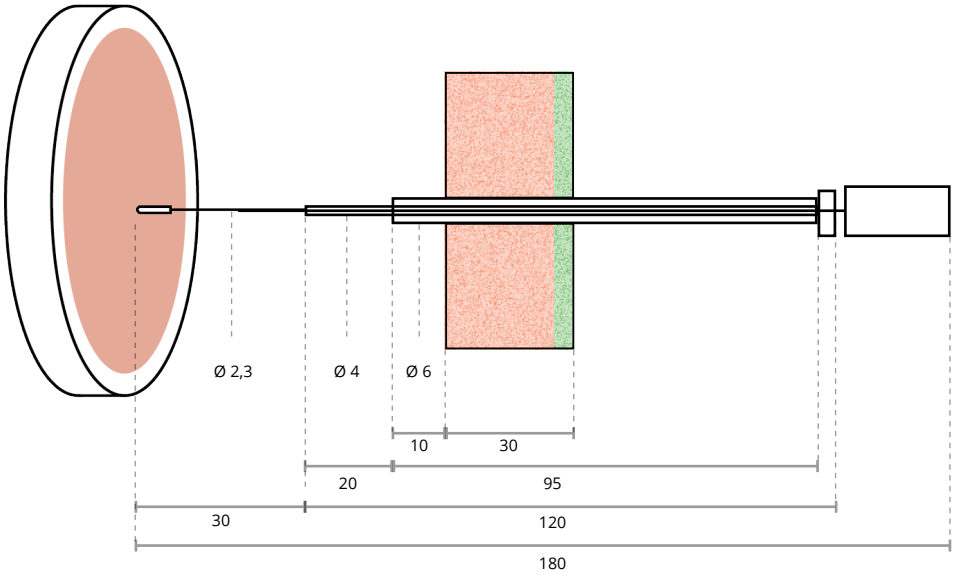


Figure 48: Set-up overview and dimensions in mm

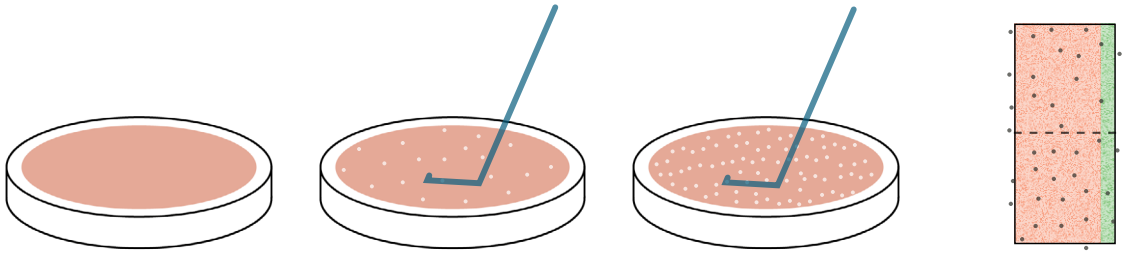
Part of the protocol is the sequence of steps that the operators needed to perform during the test. The procedure exists of 3 parts: preparing (Figure 50), executing and processing (Figure 51). The total procedure of this protocol is visualised in Appendix 17. For the test, four persons were needed. One handled the device, one held the cervix, one held the uterus and cut the swab, and one took notes.

Several blank tests were executed with a dry swab, a dry sponge and a dry run without *K. pneumoniae*. It was also checked if *K. pneumoniae* was viable. These tests are presented in Appendix 18.

Conclusion

All elements for the test execution were prepared to make sure the research question can be answered. The functional prototype will be used in the next section to execute the test and be able to answer the research question. In this test, the sampling technique will be evaluated to determine whether the product can retrieve a non-contaminated sample.

Preparing



Prepare plates for the 'uterus' (SBA 1):

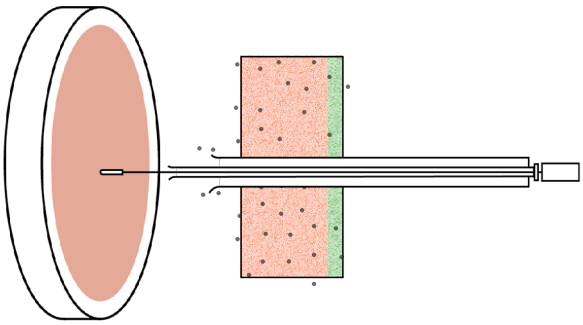
- 3 sterile SBA plates
- 3 SBA plates with *E. faecalis* (10^2/ml), 200µL spread with a Drigalski spatula
- 3 SBA plates with *E. faecalis* (10^4/ml), 200µL spread with a Drigalski spatula

Prepare sponge as the 'cervix' by cutting a line in the sponge through which the device will be inserted and infuse with TSB with *K. pneumoniae*

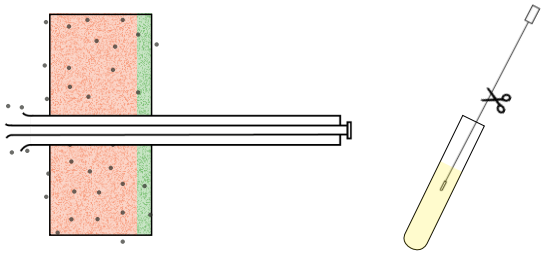
Figure 50: Procedure preparation

Executing

Part executed 9 times. Tests differ in step 5: 3 sterile, 3 E. faecalis (10^2/ml) and 3 E. faecalis (10^4/ml)

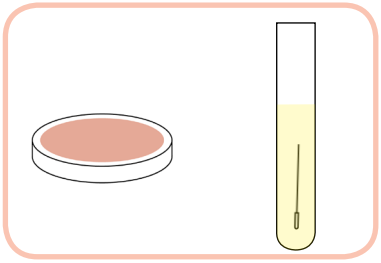


Insert device till 10mm after the cervix. Push inner tube through outer tube and swab through inner tube to open the valves to take a sample (SBA 1: sterile, *E. faecalis* (10^2/ml) or *E. faecalis* (10^4/ml))

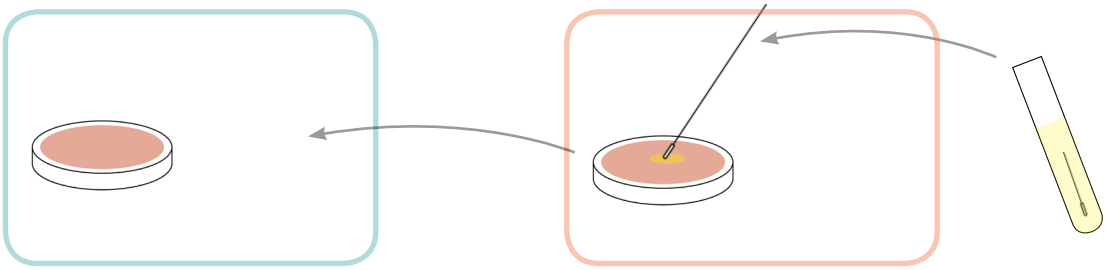


Retract the swab through the inner tube and cut the swab to release in TSB broth

Processing



Place the blood agar plate of the uterus (SBA 1) and swab in TSB Broth in a stove of 37°C for 24 hours

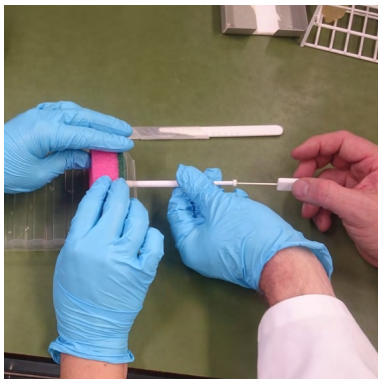


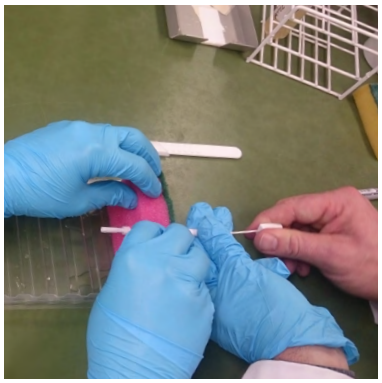
Place SBA 1 in a refrigerator of 4°C until result interpretation.
Regraft the broth of the swab with a clean swab on a new blood agar plate (SBA 2) and place in a stove of 37°C for 24 hours. Place SBA 2 in a refrigerator of 4°C until result interpretation.

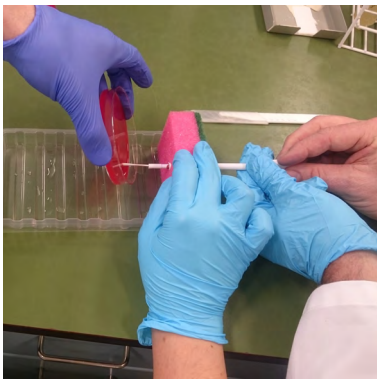
Figure 51: Procedure executing and processing

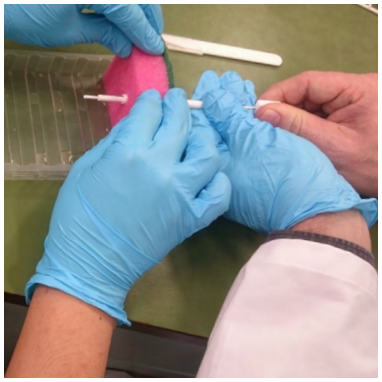
4.2 Results

Introduction
This section describes the results of the test executed at the Medical Microbiology and Infection Control Department of the Amsterdam UMC, location VUmc, on December 21st 2018. Figure 52 shows the execution of the test. A short explanation is provided to describe how to interpret the results. The results of the uterine plate (SBA 1) show whether the sampler can be inserted into the uterus without contamination. The results regrafted from the swab (SBA 2) show if the sampler can deliver a non-contaminated sample. The results will be interpreted in the following section.


Device through cervix


Extend product


Take sample of uterus


Swab back through cervix


Cut swab in TSB Broth

Figure 52: Execution of test

Explanation of results

To be able to understand the results, a short explanation of how to interpret the results is provided. Appendix 19 shows a more extended description of how to interpret the results and how the concentrations are determined.

Each of the tests has two agar plates (SBA 1 and 2) as a result. One represents the uterus (SBA 1, Figure 53) and one on which the swab is regrafted (SBA 2, Figure 54). The results show the locations that the swab came into contact with by a blue marker.

In the test, *E. faecalis* (ATCC 29212) and *K. pneumoniae* (ATCC 13883) were used. Figure 55 shows what these bacteria look like on an agar blood plate after 24h incubation in 37°C. The colonies of *E. faecalis* are visible as small white dots. The concentration of *E. faecalis* was determined and noted in the colony-forming unit (CFU). This is the concentration per millilitre. The colonies of *K. pneumoniae* are larger and slimier than the colonies of *E. faecalis*. No contamination took place when there is no *K. pneumoniae* present in the results.

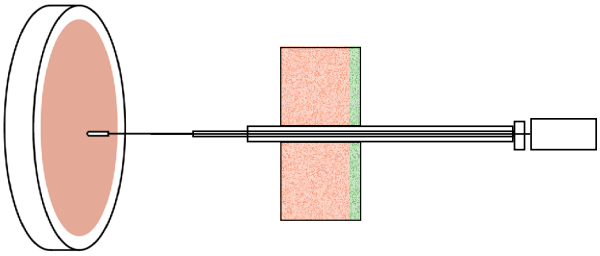


Figure 53: SBA 1 representing the uterus

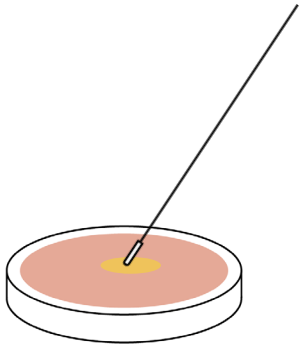
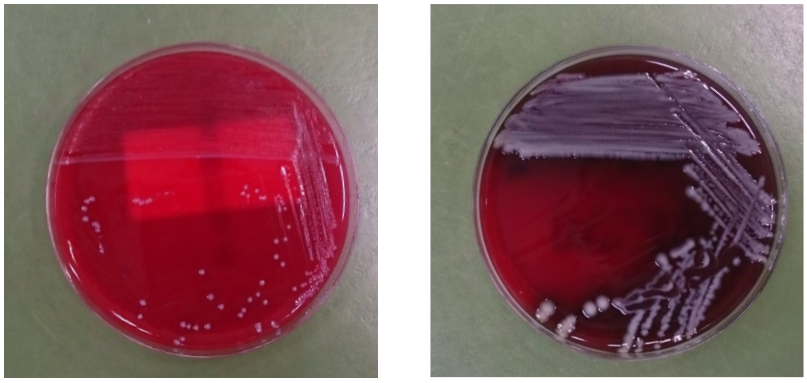


Figure 54: SBA 2 representing the regrafted swab

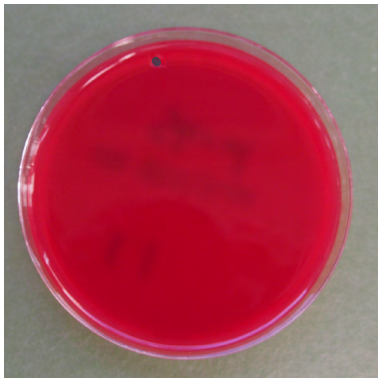


E. faecalis (ATCC 29212)

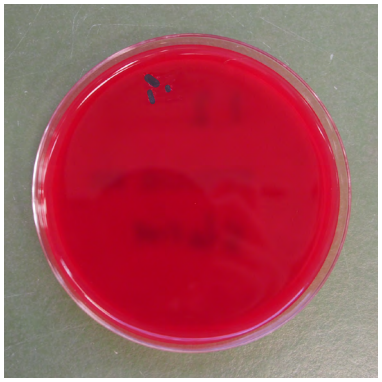
K. pneumoniae (ATCC 13883)

Figure 55: Reference of bacteria

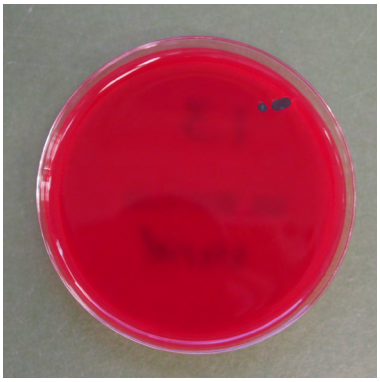
Results of uterus (SBA 1)
In Figure 56 the results from the blood agar plates of the uterus (SBA 1) are presented.



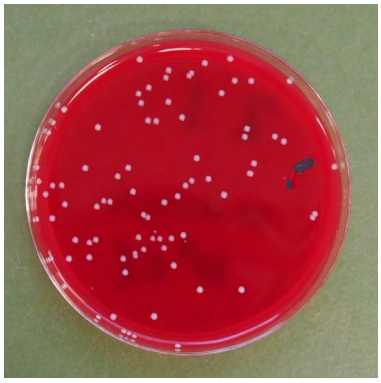
1.1 Sterile
Inner valve slightly got loose
No growth of bacteria



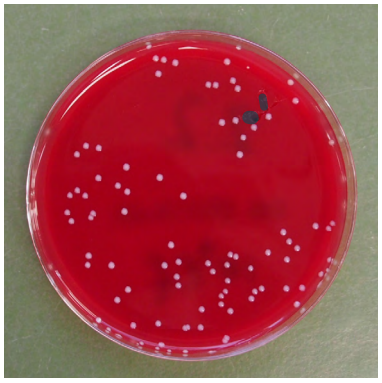
1.2 Sterile
Prototype functioned as intended
No growth of bacteria



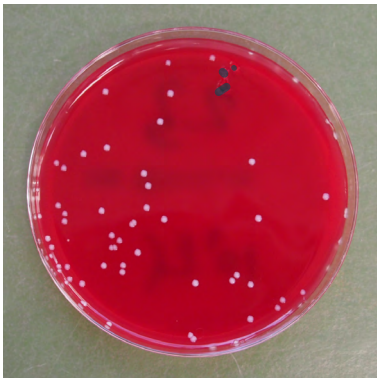
1.3 Sterile
Prototype functioned as intended
No growth of bacteria



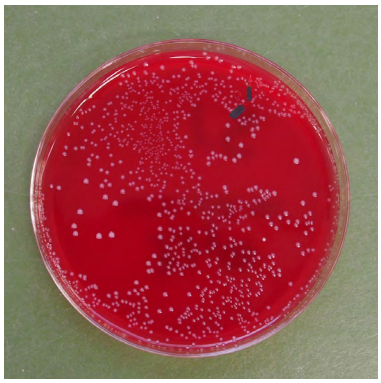
2.1 *E. faecalis* 10^2/ml
Inner valve slightly got loose
E. faecalis concentration $10^{2,6}$CFU/ml (83 colonies)
No *K. pneumoniae* present



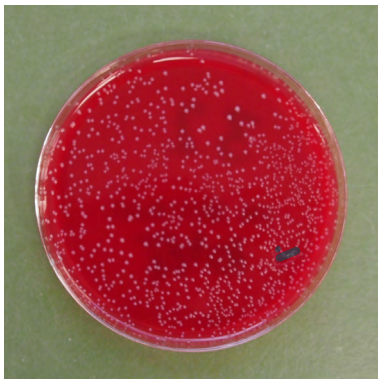
2.2 *E. faecalis* 10^2/ml
Prototype functioned as intended
E. faecalis concentration $10^{2,6}$CFU/ml (91 colonies)
No *K. pneumoniae* present



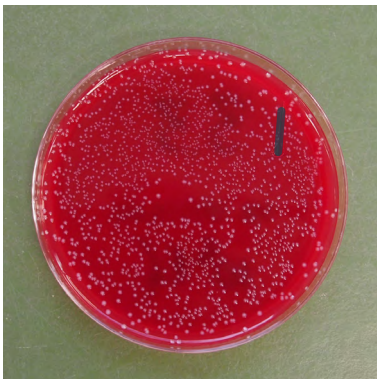
2.3 *E. faecalis* 10^2/ml
Prototype functioned as intended
E. faecalis concentration $10^{2,5}$CFU/ml (65 colonies)
No *K. pneumoniae* present



3.1 *E. faecalis* 10^4/ml
Inner valve stuck at tip swab
E. faecalis concentration $10^{3,8}$CFU/ml (1278 colonies)
No *K. pneumoniae* present



3.2 *E. faecalis* 10^4/ml
Prototype functioned as intended
E. faecalis concentration $10^{3,8}$CFU/ml (1341 colonies)
No *K. pneumoniae* present

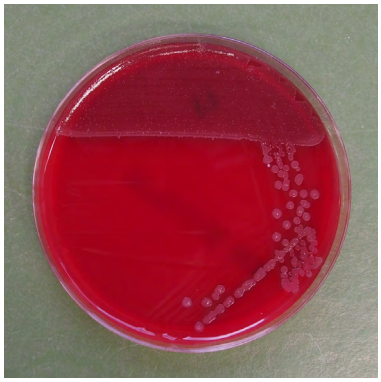


3.3 *E. faecalis* 10^4/ml
Prototype functioned as intended
E. faecalis concentration 10^4CFU/ml (1861 colonies)
No *K. pneumoniae* present

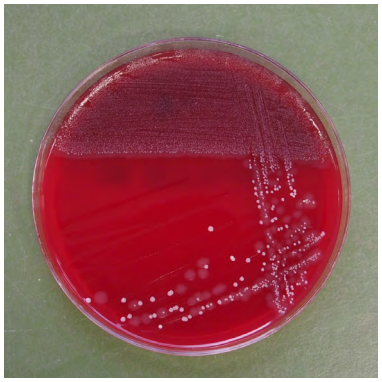
Figure 56: Results of uterus (SBA 1) with marked location where swab took sample

Results regrafted from swab (SBA 2)

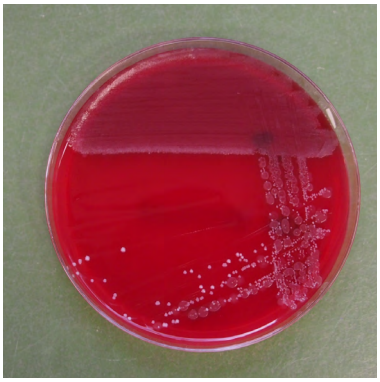
In Figure 57 the results from the blood agar plates (SBA 2) regrafted from the swab are presented.



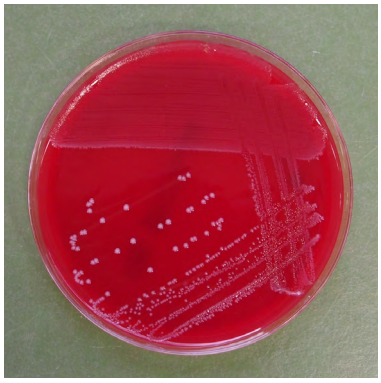
1.1 Sterile
Inner valve slightly got loose
No *K. pneumoniae* present
Mixed flora with gram-positive bacteria



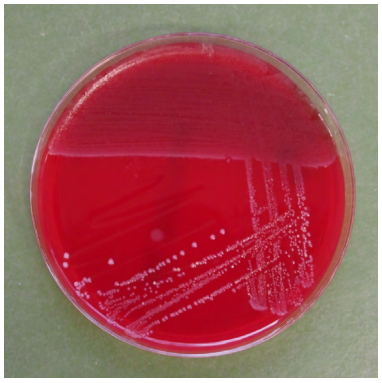
1.2 Sterile
Prototype functioned as intended
No *K. pneumoniae* present
Mixed flora with gram-positive and gram-negative bacteria



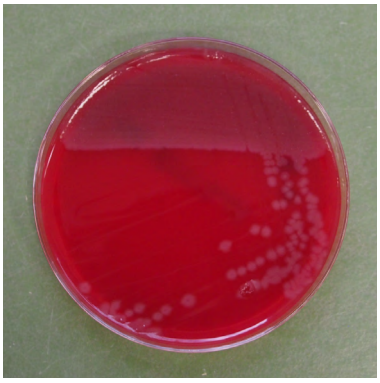
1.3 Sterile
Prototype functioned as intended
No *K. pneumoniae* present
Mixed flora with gram-positive and gram-negative bacteria



2.1 *E. faecalis* 10^2/ml
Inner valve slightly got loose
No *K. pneumoniae* present
E. faecalis present

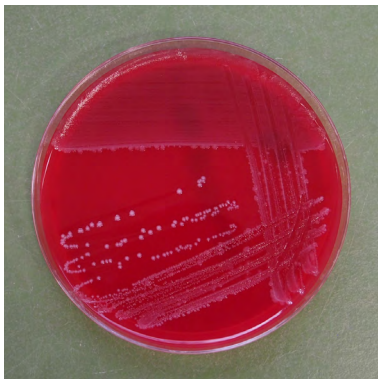


2.2 *E. faecalis* 10^2/ml
Prototype functioned as intended
No *K. pneumoniae* present
Mixed flora with *E. faecalis* and other gram-positive bacteria

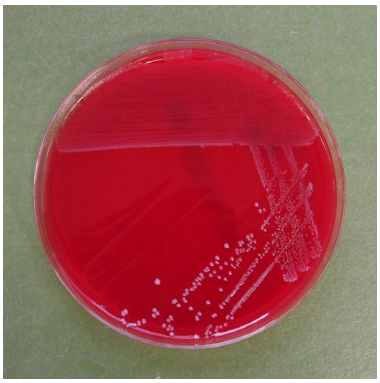


2.3 *E. faecalis* 10^2/ml
Prototype functioned as intended
No *K. pneumoniae*
No *E. faecalis* present
Mixed flora with gram-positive and gram-negative bacteria

3.1 *E. faecalis* 10^4/ml
Inner valve stuck at tip swab
Presence of *K. pneumoniae* (2 colonies)
E. faecalis present



3.2 *E. faecalis* 10^4/ml
Prototype functioned as intended
No *K. pneumoniae* present
E. faecalis present



3.3 *E. faecalis* 10^4/ml
Prototype functioned as intended
No *K. pneumoniae* present
E. faecalis present

Figure 57: Results regrafted from swab (SBA 2)

Test 3.1 resulted in contamination on SBA 2, Figure 58. Therefore, further attention will be given to this particular test. In Figure 59, the contamination is zoomed in on, showing the two colonies of *K. pneumoniae* present.

During this test 3.1, the inner valve fell off completely. The inner valve and its connection got stuck on the tip of the swab, Figure 60. To be able to continue the test, the swab was retracted to make the valve come off and then the valve fell off completely, Figure 61.

Conclusion

The results show two main insights. In all nine tests, there was no contamination on the blood agar plate of the uterus. In eight out of nine tests, the sampler was able to deliver a non-contaminated sample. There was a prototype fail in the test with contamination. In the next section, the test will be concluded.

Figure 58: Results 3.1 regrafted from swab (SBA 2)

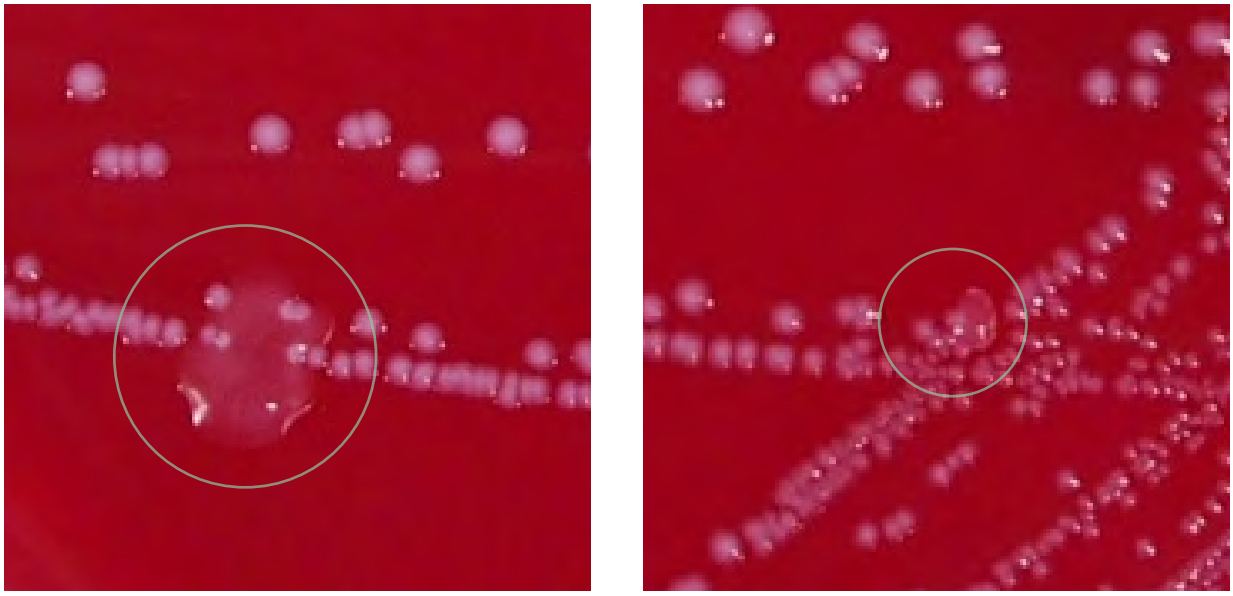


Figure 59: Zoom in contaminations on 3.1 SBA 2

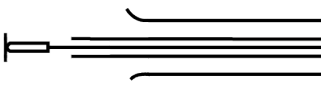


Figure 60: 3.1 Valve stuck on tip

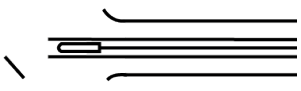


Figure 61: 3.1 Swab retracted to let valve come off

4.3 Conclusion test

Introduction
This section concludes the results from the test of the previous section. The main conclusion is the answer to the research question. The test showed that the prototype of the sampling technique was able to take a non-contaminated sample. The section concludes specifically on the blank tests, the sterile uterus, the uterus with *E. faecalis* 10^2/ml and the uterus with *E. faecalis* 10^4/ml. In the rest of the phase, the test will be further evaluated.

Blank tests
From the blank tests it could be concluded that no *K. pneumoniae* was present on one of the used materials for the test. Other mixed flora were present on the materials. This mixed flora was probably skin flora from handling the materials, oral flora from talking and breathing of the operators during the procedure and bacteria that were present on the materials beforehand. In another blank test, *K. pneumoniae* was sampled and incubated, which showed *K. pneumoniae* was viable. Finally was evaluated that the procedure could take a sample of *E. faecalis.*

Sterile uterus
The uteri of this test (SBA 1) were sterile at the beginning of the test, and the test showed the swab did not bring bacteria, especially no *K. pneumoniae*, to the uterus during sampling.

The regrafted blood agar plates (SBA 2) showed no presence of *K. pneumoniae*. From this result it can be concluded that no contamination from the cervix took place during inserting and exiting the uterus. Other mixed flora were present, of which the origin is explained in the blank test.

Uterus with *E. faecalis* 10^2/ml
All of the blood agar plates of the uterus (SBA 1) showed approximately the same concentration of *E. faecalis* as initially intended. The determination of the concentration is shown in Appendix 19. On the plates, no other bacteria were shown. It showed that the swab did not bring bacteria, especially no *K. pneumoniae*, to the uterus during sampling.

The regrafted blood agar plates (SBA 2) showed no presence of *K. pneumoniae*. From this it can be concluded that no contamination from the cervix took place during inserting and exiting the uterus. Two of the three regrafted plates contained *E. faecalis* as sampled in the uterus. One of the three regrafted plates did not contain *E. faecalis*. It is possible the swab did not touch one of the bacteria on the blood agar plate of the uterus. The other reason could be that other bacteria from the presently mixed flora had overgrown *E. faecalis*.

Uterus with *E. faecalis* 10^4/ml
All of the blood agar plates of the uterus (SBA 1) showed approximately the same concentration of *E. faecalis* as initially intended. Only one of the three plates showed a slightly unequal distribution of colonies. On the plates no other bacteria were shown. It showed the swab did not bring bacteria, especially no *K. pneumoniae*, to the uterus during sampling.

In two of the three tests, the regrafted blood agar plates (SBA 2) showed no presence of *K. pneumoniae*. From this it can be concluded that no contamination from the cervix took place during inserting and exiting the uterus. On one of the three regrafted blood agar plates two colonies of *K. pneumoniae* were present. During this test, the prototype failed. The connection part of the silicon valve came off and got stuck on the tip of the swab. To be able to continue with the test, the swab had to be retracted to make the inner valve come off and allow the swab to take a sample. A reasonable possibility is that the swab got contaminated during this procedure due to the presence of *K. pneumoniae* on the inner tube or the outer tube. It is interesting to notice that a malfunction in the prototype resulted in contamination. It is also reassuring to see that contamination was a possible result of the tests and that the set-up was not unintentionally biased towards providing the intended results. On all of the regrafted blood agar plates, other mixed flora were present.

Conclusion
In general, it can be concluded that this sampling technique can take a non-contaminated sample. The sampling technique was tested with a 2:1 prototype in an In Vitro Test. The test showed how the prototype would take a sample of the bacteria in the uterus. In one test the tip with the inner valve got completely loose, and in two other tests the inner valve got slightly loose. These aspects need to be improved and tested to be able to have a non-contaminated sample and to ensure patient safety. In the next section, the potential drawbacks of the test will be discussed.

4.4 Discussion

Introduction
This section addresses the most significant drawbacks of the test. The following aspects are discussed: not all materials were sterilised beforehand, the scale of the prototype, the presence of enterococci in the blank test of the *K. pneumoniae* and the representation of real life provided by the In Vitro Test. These drawbacks will be used to generate recommendations for follow-up tests and the design of the sampler.

Non-sterile materials
Not all used materials were sterilised beforehand due to the technical drawbacks of the prototype. Other bacteria than intended were therefore present in the results. These bacteria could have outnumbered the bacteria that were considered as contamination. TSB was used as a culture broth to grow the low abundance of bacteria. In TSB the bacteria with the highest load will multiply the fastest. Therefore it is possible that bacteria with a higher load could have overgrown bacteria with a lower load. A malfunction in one of the prototypes, which resulted in a contaminated sample, could disprove this statement.

Prototype made on scale 2:1
The prototype is built on another scale than designed in the concept, a 2:1 scale. The length of the prototype has intentionally not been scaled along. This is done for the ease of handling during the test because it did not need to exceed the length of a vagina as during a gynaecological intervention. The functionality of the product could differ on a 1:1 scale.

Enterococci in blank test
On the blank test of the *K. pneumoniae* other bacteria were also shown, probably enterococci. Enterococci are gram-positive bacteria, of which *E. faecalis* is a common species in the intestines of humans. On the sponge not only *K. pneumoniae*, but also enterococci were present. It was unknown what species of enterococci were present. In the regrafted results from the swab (SBA 2) enterococci were also present in the mixed flora. There is a chance that the enterococci present in the mixed flora on SBA 2 were not *E. faecalis* sampled from the uterus, but from contamination with the sponge. There is not much chance that this happened because on 8 of the 9 SBA 2 plates there was no K. pneumoniae present from the sponge.

In vitro representation
The test set-up of the uterus attempted to be as representative as possible, but will always be a representation of the real-life situation. Inside the female body, the walls of the uterus would result in a pressure on the prototype during inserting, which was not the case in this study. Other aspects, like the concentration of bacteria in the uterus, could also differ from the real-life situation.

Conclusion
In general, this study showed that the sampling technique could take a non-contaminated sample. If this technique is further developed and made safer for the patient, it could contribute to research into the existence of a uterine microbiome and its possible relation to (sub)fertility. The discussion is the basis for the next section. In this section, the recommendations for follow-up studies and the design of the sampler will be made.

4.5 Recommendations

Introduction
The test resulted in recommendations for follow-up studies and the design of the sampler. These recommendations derived from the test and Expert Evaluation with the microbiologists. The most important ones are listed in this section. In the next phase, the recommendations of the sampler will be applied in the design of a research sampler.

Follow-up studies
From this study, there are several recommendations for follow-up studies. The most interesting follow-up directions are a study with all materials sterilised beforehand, a study with prototypes on scale 1:1 and an in vivo study.

First of all, a study with all materials and instruments sterilised would be recommended. Due to the technical drawbacks of the prototype, it was hard to sterilise. A different prototype with other connections and materials would make it easier to ensure no other bacteria were already present on the device. Also, even more careful execution of the test could decrease the presence of contaminating bacteria. If all instruments were sterile, it would reduce the chance for overgrowth of other bacteria. Therefore, the bacteria from the contamination site could not be outnumbered during culturing in the broth.

A follow-up study could be executed with a prototype on scale 1:1. A prototype on scale 1:1 would test the possibilities for its manufacturability and whether the principle still functions on a real-life scale. Especially the type of valves and the connection of the valves to the rest of the product is a point of attention.

If a 1:1 study would be successful, an in vivo study would be interesting as a follow-up. In vivo refers to experimentation using a whole, living organism. Testing the device inside the uterus would give more information about the functionality of the device and the usability for gynaecologists. An in vivo study would finally give more insight into what is actually going on in the uterus. Maybe there is no uterine microbiome, but researchers were only measuring contamination of the cervix and calling it a uterine microbiome. Therefore, ultimately it would be most interesting to use this sampling technique to study the relation of the uterine microbiome and (sub)fertility.

Design of sampler

The study resulted in several recommendations regarding the design of the sampler. The most important points of attention are to the valves, the ability to sterilise the device, the inability of retracting the inner tube along with the swab, changes to a 1:1 prototype and tactile feedback to the end-user while using the device.

The main recommendation is to change the valves at the tip of the prototype and find another solution for this connection. The valves were the main issue during the study, and the inner valve sometimes came (partly) off from the device. This resulted in the possibility of contamination during sampling but is also highly undesirable regarding patient safety. Currently, the silicon valve is connected 3mm below the tip of the device due to technical reasons. This creates a kind of container at the tip where mucus with bacteria can be collected. It is recommended to have the valve at the tip to decrease the chance of contamination via the valves. Therefore a secure connection of a valve at the tip of the device is of importance for a safe, non-contaminated sampling procedure.

The sampler needs to be able to be sterilised, for example by an autoclave. During further embodying the device, the materials and connections need to be able to withstand the temperature and pressure of the sterilisation technique to have no unintended contaminating bacteria present.

When the operator of the product pulled back the swab, the inner tube would go back along. It is of importance the inner tube will stay extended to make sure the swab has the least chance of contamination via the outer valve and outer tube. A blockade to prevent the inner tube being pulled back along when retracting the swab would decrease the chance of contamination during exiting the uterus.

Another recommendation is regarding dimensions of the product on a scale of 1:1. The swab needs to have a large area to be able to take a sample. The microbiologists recommend flocked swabs for sampling. Therefore it is of importance to keep the diameter of the swab as large as possible while maintaining the diameter of the total product as small as possible for patient comfort. This could be achieved by having a thin, strong wall for the inner and outer tube.

During the study, the operator noticed when a valve was open or closed. This feedback was perceived as reassuring, and this kind of tactile feedback should be maintained in further studies and prototypes.

Conclusion

The recommendations for follow-up tests are for further studies on this sampler, but will not be a part of this graduation thesis. The recommendations for the sampler will be taken along to the next phase. In the next phase, the conclusions of the test will come together in the final product and its context.

5. DELIVER

In the final phase of the thesis, the main findings of the project are concluded. The recommendations of the test and Expert Evaluations all come together in the advice for a research sampler. This sampler is needed to first understand the link of the uterine microbiome and (sub)fertility. Subsequently, the design of a commercialised sampler for a specific use case can be focused on. From this project takeaways for designers and engineers working on related projects are listed. Finally, the conclusion shows the final thoughts on the initial design goal, the further project recommendations and personal evaluation.

5.1 Research sampling device

Introduction

The test showed that the designed sampling technique could take a non-contaminated sample. Further research is needed after this graduation to be able to conclude if there is a link between the uterine microbiome to fertility. Therefore, advice for a research sampler is made. A Storyboard shows how the design would function in the female body. A risk analysis is performed, and recommendations are provided to help mitigate these risks. Finally, use cases are set up to have an overview of the specific use cases in which the sampling technique can be used. The next section lists takeaways for similar projects and the continuation of this project after the thesis.

Advice for design of research sampler

Further research must show if there is a link to the uterine microbiome and subfertility. In this research, the uterine microbiome of, for example, 100 patients should be sampled to be able to draw conclusions of its possible link to subfertility. The test showed proof of principle for the design technique. The recommendations of this test and the experts have been combined to provide advice for the design of a research sampler.

Figure 62: Reusable

Figure 63: Disposable

Figure 64: Reposable

There are three main variants in which the product can be prototyped. The device can be a reusable, a disposable or a reposable device. Each of them will be explained shortly. In the figures, the blue parts show the disposable parts and the orange parts show the reusable parts.

- Reusable (Figure 62): All parts of the device are reusable, except for the swab. The rest of the device needs to be able to be sterilised. The sampling technique needs to be slightly altered because the design of the valves can currently only be used once. Since each test in the research is performed in the same way, there is less inter-test variability. 5 to 10 prototypes are needed to execute the tests.
- Disposable (Figure 63): The total device is only used once and disposed of afterwards. In a disposable version, the functionality of the device and the closure of the valves can be guaranteed since each product is only used once. It is quite expensive to set up production for such a small number of products. 100-150 prototypes are required and small production facilities need to be set up.
- Reposable (Figure 64): Some parts of the device are reusable, and some parts are disposable. The reusable base parts need to be sterilised in between patients. The parts that are important for the functionality are disposable and changed between the patients. 5 to 10 reusable base parts are needed, and 100-150 disposable parts are required.

From an evaluation with a medical design engineer and a sterilisation expert of the UMC Utrecht, it is concluded that it would be best to start with a reposable version of the product. The base parts are made of metal and can be sterilised in an autoclave. The valves and swabs are disposable. The combination of reusable and disposable parts guarantee safety and functionality, while still being affordable for a small batch size (Belluche, 2017).

A set up of a possible design is made in Figure 65. The main findings from the test and expert consults are combined in this design. The design should be further evaluated, prototyped and tested before in vivo tests can be executed. In particular, more extensive research is needed into the disposable parts. This will provide a better understanding of which parts would reduce the initial production costs and allow the functionality of the product to be tested. During prototyping, several suppliers are contacted. The most interesting suppliers and some of their product samples are listed in Appendix 20.

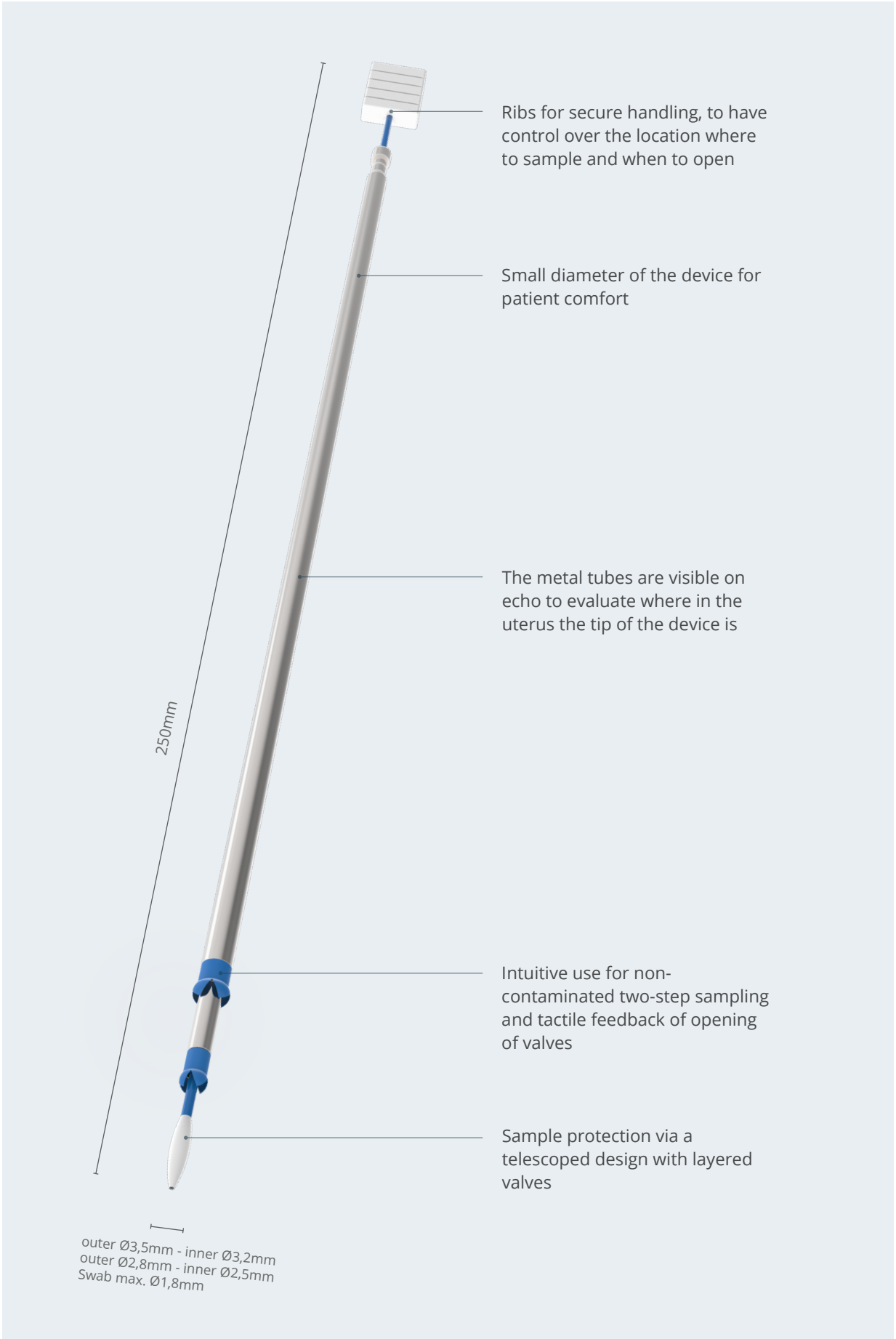


Figure 65: Research device design overview

Figure 66 shows how the valves are connected to the metal tubes. By sliding the valve on the tip, the rib will slide into the groove, and the valve is connected. The swab is protected by two of these valves on top of the inner and outer tube. Figure 67 shows a section view of the closed tip. A flocked swab is used to sample the bacteria, which is less painful for the patient than via suction like the Pipelle (Cook Medical, 2018). Figure 68 shows an open outer valve and a closed inner valve with a pre-perforated X-shape incision.

The device will be inserted through the cervix of the patient. The gynaecologist can evaluate when the device has passed the internal ostium by using an echo because the metal will be visible on echography. The outer diameter and inner diameter of the tubes are based on the dimension of standard stainless steel capillary tubes (Salomon's Metalen, 2019). At the end of the inner tube, a stop is connected to prevent the inner tube from sliding through the outer tube. The handle functions as a stop to prevent the swab from sliding completely through the inner tube. After usage, the valves are disconnected and disposed of. The tubes can be sterilised, as it is possible to sterilise tubes larger than 1mm (sterilisation expert of the UMC Utrecht, personal communication, January 23, 2019).

Figure 66: Connection valve to tip

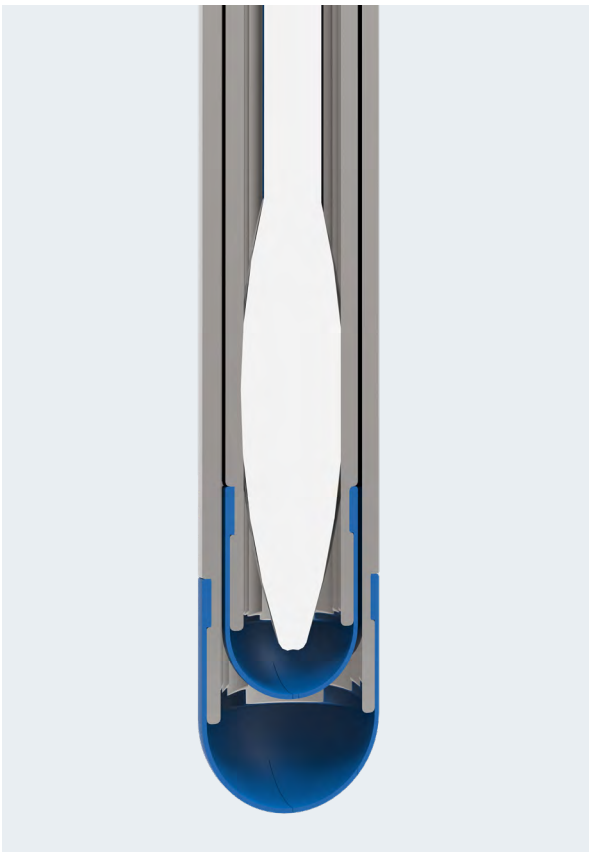
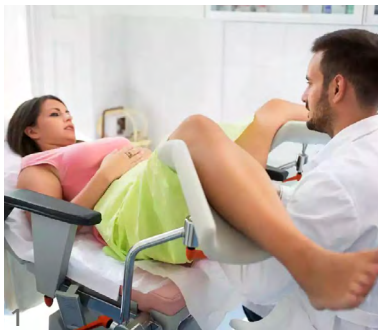


Figure 67: Section view of the tip

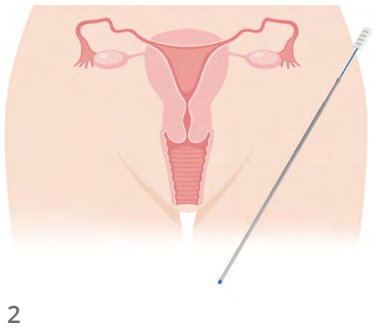
Figure 68: Valve open and closed

Storyboard of use

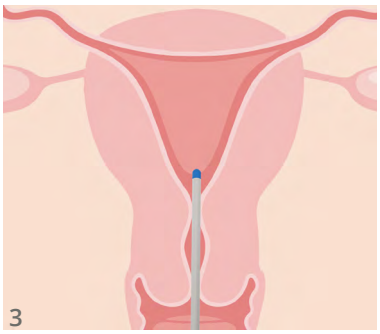
In the test, the prototype was used in an in vitro representation of real-life. The research sampler would be used in a real-life test to understand the relation of the uterine microbiome and fertility. This is done by taking a sample of the uterine microbiome as is explained by a general storyboard of use, shown in Figure 69. The Storyboard consists of three main steps: the patient is prepared; the device takes a sample; and the sample is analyzed for research purposes. Depending on the research question and set up, the Storyboard would become more specific.



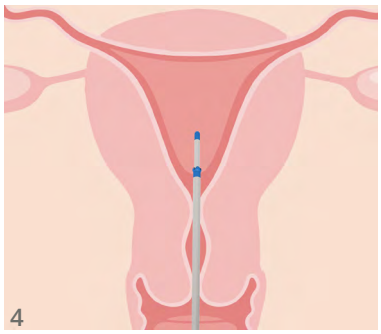
Explanation procedure (Didesign, 2019)



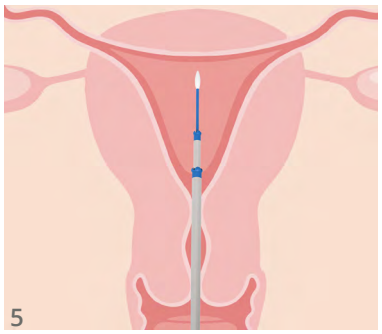
Prepare patient and sampler



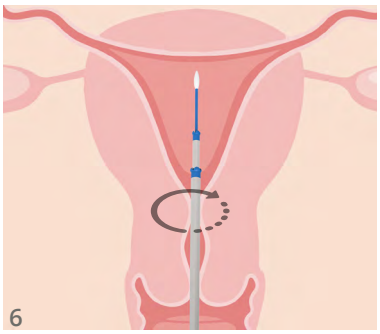
Insert sampler till after internal ostium



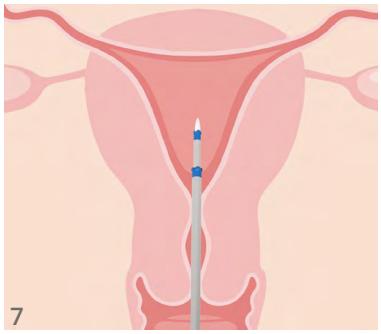
Extend tube and open outer valve



Extend swab and open inner valve

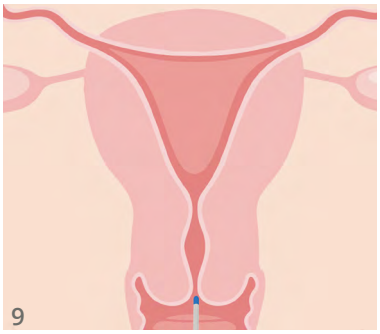


Turn swab to take sample

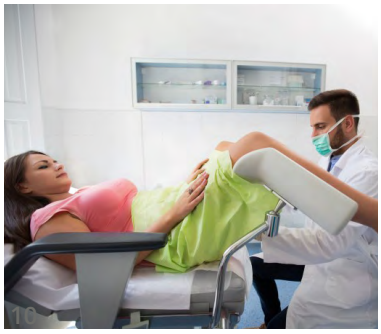


Retract swab

Deliver sample (Didesign, 2019)

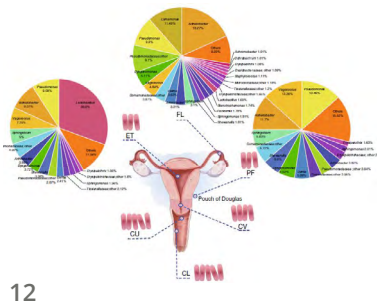


Remove rest of sampler



Aftercare patient (Didesign, 2019)

Next-Generation Sequencing for results (Didesign, 2019)



Conclusion research (Chen et al., 2017)

Figure 69: Storyboard of use

Risk analysis

The Risk Analysis is based on a Failure Mode and Effect Analysis (FMEA) to determine which risks should be considered in the final design or should be of importance for further development (Six Sigma, 2017). This analysis shows what should be changed in the final concept to make sure the risk of this potential failure is as low as possible. The risks that are determined are set in context with similar gynaecological procedures. Minor bleeding is not uncommon during, for example, the placement of an intrauterine device, so these risks have not been taken into account in this FMEA.

A Risk Priority Number (RPN) has been calculated, to identify the risk of a specific action or component (Institute of Healthcare Improvement, 2017). The RPN is a result of multiplying the severity with the frequency of occurrence and the ability to detect the failure mode. Figure 70 shows the main risks of the uterine microbiome sampler. The risks with the highest RPN and the risks with a high severity (9 or 10) will need extra attention in the future design. Some of the recommendations have been already implemented in the design of the research sampler, and others should be taken along for further product development.

Rank	Failure mode	Failure effect	RPN	Severity	Occurrence	Detection	Recommendations
1	Talking and breathing on the product	Sample is contaminated	**441**	7	7	9	Instruction and blank tests
2	Gynaecologist touches product wrong place	Sample is contaminated	**378**	7	6	9	Instruction, blank tests, protective packaging
3	Valve got loose from product	Valve stays behind in uterus	300	**10**	5	6	Check parts afterwards, secure connection
4	Sampler still in cervix during sampling	Unreliable results without knowing	294	7	6	7	Echo marker to know when in uterus
5	Sharp edges product	Pierce through uterus	280	**10**	4	7	Flexible product with smooth fillets
6	Valve partly comes off	Sample is contaminated	252	7	6	6	Check parts afterwards, secure connection
7	Swab not in inner tube retracted	Sample is contaminated	210	7	5	6	Blockade on inner tube to prevent sliding along with swab
7	Valve opened before in the uterus	Sample is contaminated	210	7	5	6	Design a valve that is still a little closed beforehand
8	Swab breaks during sampling	Part of swab stays behind in uterus	180	**10**	3	6	Check parts afterwards, select strong swab
9	Sample too small for microbiome research	No proper conclusion of analysis	40	5	4	2	Instruction, use flocked swabs
9	Valve does not open	Not possible to take a sample	40	5	4	2	Design a valve that opens easily

Figure 70: FMEA

Use cases

In this thesis has been focused on the sampling of the uterine microbiome for fertility research. More specific use cases generate an overview of the scenarios in which the product can be used, as is shown in the text boxes below. If more information about the uterine microbiome is available, a more detailed business case can be set up. The use cases are based on current uterine microbiome literature in general.

Conclusion

Advice for a research sampler has been based on experience during the In Vitro Test with the prototype, the test results and recommendations of experts. The design is a rough set up and needs to be further elaborated upon, evaluated with experts and tested for in vivo research. In the Storyboard, the use of the product has been explained. However, the steps will differ depending on the type of research. The main risks during further research are of importance for additional recommendations. Use cases have been listed and define the potential applications of the sampling technique. In the next section, the main takeaways will be listed for related projects. These takeaways are also of importance for further development of the research sampler.

Use case 1: Increase success rate pregnancy of subfertile woman

The uterine microbiome can be sampled to understand the possible relation of the uterine microbiome and subfertility. Currently 20.000 Dutch couples a year are confronted with subfertility (Freya, 2017). If there is a relation between the uterine microbiome and subfertility, there could be a kind of differentiation of fertile, infertile and subfertile microbiomes. Subsequently, research is needed to know if the success rate of pregnancy can be increased by changing the uterine microbiome.

Use case 2: Detection and treatment of other gynaecological disorders

The uterine microbiome can be of interest for other gynaecological disorders as well. There are currently many other gynaecological disorders that do not have a clear cause. Research is showing other possible relations with the uterine microbiome, for example with pelvic inflammatory disease (Cover, 2012; Haggerty & Ness, 2007) and dysfunctional menstrual bleeding (Pelzer, Willner, Buttini, & Huygens, 2018). The product can be used to research a relation of the uterine microbiome and other gynaecological disorders.

Use case 3: Increase success rate of ART

If the sampling technique can be used to enter a uterus with a minimum of contamination, it could be beneficial to improve the success rate of ART. Each year, over 14.000 IVF/ICSI treatments are executed (NVOG, 2017) with average costs of €2.500 per treatment (Radboud UMC, 2010). Currently, the uterus becomes contaminated when a product is inserted during, for example, intrauterine insemination, IVF or ICSI. This highly contaminated uterus could have an adverse effect on the success of the ART. Therefore the product could be possibly used to insert an embryo or sperm without contaminating the uterus with bacteria from the cervix.

Use case 4: Sampling microbiomes beyond gynaecology

Finally, the sampling technique can be used for cases beyond the gynaecological field. An example could be for sampling the gut microbiome without contamination (Pollock, Glendinning, Wisedchanwet, & Watson, 2018). However, no further research has been conducted into this use case.

5.2 Takeaways for related projects

Introduction

Over the last few years, research has provided a better understanding of the potential link between the human microbiome and several disorders. Instruments that can sample, test, understand or change a specific microbiome are therefore very relevant. The field of microbiology is new for most engineers and designers. Therefore, the main takeaways from this study are summarised in guidelines to be able to build upon each other's work as designers and engineers. The guidelines are also of importance for further development of the uterine microbiome sampler. The next section will conclude the project in total.

Prior knowledge

Prior knowledge is of importance before a designer or engineer starts with a similar project. These aspects are listed in Figure 71 and should be taken into account during the entire project.

Analyse and design

During the analysis and design phase, the designer or engineer should get a hold on what the main problem is, what the suitable solutions are and what risks should be mitigated. Figure 72 lists the main aspects that are of importance during the analysis and design phase.

Bacteria are everywhere. When the operator talks or touches something, bacteria are transferred. Contamination is binary. A little contamination is not acceptable. Little contamination is still an enormous amount of bacteria, especially after a while in a favourable environment. So, something is contaminated, or not.

Especially when working with low biomass samples or samples from a low abundance site, a little contamination could lead to misleading conclusions in tests. Therefore it is of importance to follow strict protocols and make the design as foolproof as possible.

Differences in bacterial loads are often logarithmic. When sampling a low-load environment (e.g. 10^2 bacteria/ml) after passing through a high-load environment (e.g. 10^{11} bacteria/ml), even a million-fold dilution of the contaminant will leave the contaminant to outnumber the bacteria from the low-load environment by a factor of 1000.

Make sure everything is documented and verified according to the regulations of the industry of the product. For medical products is the medical classification according to the MDR of importance.

Figure 71: Prior knowledge

Set up a list of main functions that the product needs to fulfil. These functions will be the basis of the list of requirements and will be updated together with the rest of the findings during the process.

Generate an extensive Risk Analysis. Formulate what can go wrong with the design ideas and what kind of role contamination plays in the functionality of the product. For example, is non-contamination of importance for patient safety or the interpretation of a sample? Formulate mitigations to minimise these risks.

Verify the assumptions and design with microbiologists who are experts in the industry of the product. This will lower the chance of misconceptions and disappointments in a later stage.

Use Three-Dimensional Modelling as the first verification of the design. Execute a test on this prototype with materials at hand that can mimic the spread of bacteria, for example, colouring agent in water, gel or syrup.

Figure 72: Analyse and design

Verify
Figure 73 shows how assumptions can be verified during the analysis and design phases. A test should be conducted with a research question and a functional prototype should be made to execute the test.

Towards usage
When the product is proceeding towards usage, the (medical) regulations need to be respected, and user safety is of most importance. Figure 74 lists the main aspects that should be considered before the product is used.

Conclusion
For the continuation of this project or the start of a similar project, the takeaways from this project could be interesting to use as a starting point. Each project and process is different, but at the start of this thesis there was no overview of takeaways from previous related projects. In the next section, the graduation thesis will be concluded on the design goal, project recommendations and personal evaluation.

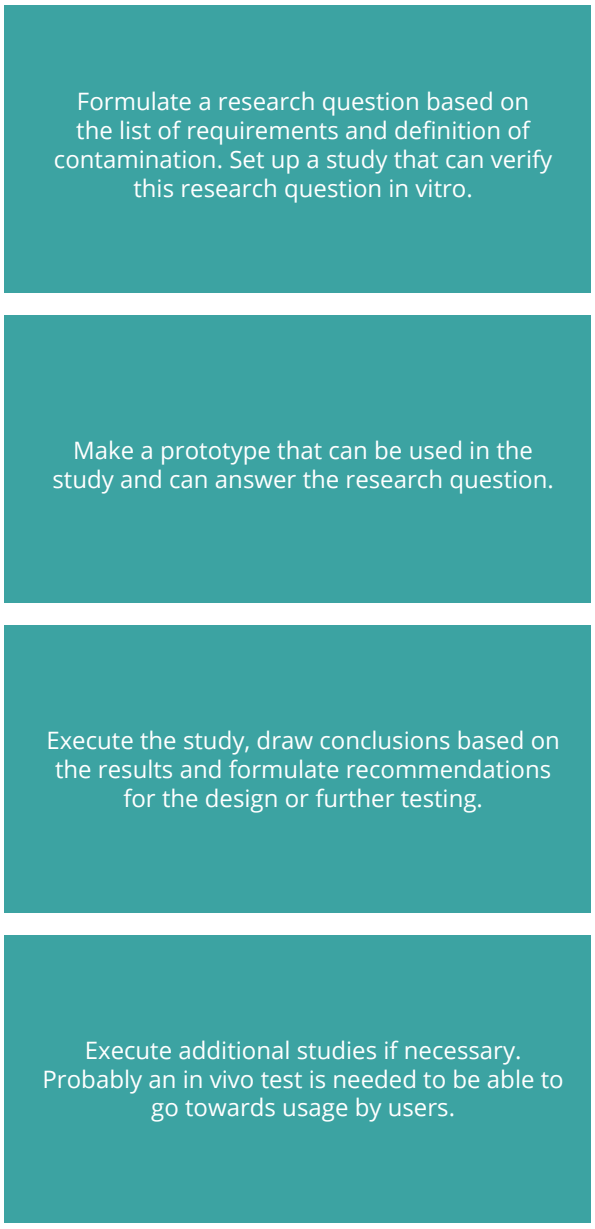


Figure 73: Verify

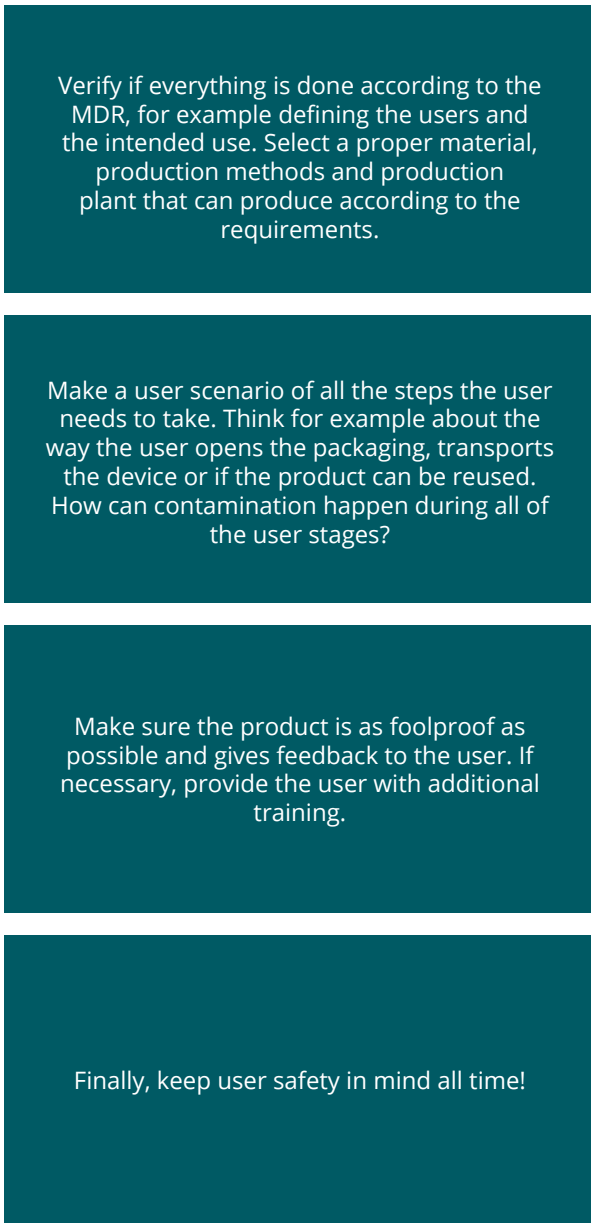


Figure 74: Towards usage

5.3 Concluding

Introduction
This section lists the concluding thoughts of the graduation thesis. First, the conclusions on the design goal are drawn. The sampling technique has fulfilled the proof of principle, showing that the idea has the potential to take a non-contaminated sample. Different developments are required in order to further develop the sampling technique into a product for research or commercial use. These possible development steps are listed in the project recommendations. Finally, the project will be evaluated and reflected on, based on the learning goals.

Conclusion design goal
The scope of this graduation project was to design a sampler that can take a non-contaminated sample of the uterine microbiome for fertility research. There is currently no medical device that has been proven to take a non-contaminated sample of the uterine microbiome. This hinders research concerning the relation of the uterine microbiome and (sub)fertility. The goal was to design a sampler that can take a sample of the uterine microbiome without contamination for research concerning the relation of the uterine microbiome and (sub)fertility. During the project, the focus shifted more towards the proof of principle of the sampling technique instead of the design of the sampler.

The designed sampler is a telescope layered product that extends into the uterus of the patient. A swab is protected by two tubes, and each tube is protected with flexible valves for contamination prevention. The gynaecologist has control over the moment the product opens and the location of sampling. By taking a sample with a brush, the sampling procedure will be less painful for the patient. The sample can be used for modern microbiological research like Next-Generation Sequencing.

Functional prototypes of the sampling technique on a scale of 2:1 have been built. These prototypes have been tested in an In Vitro Test at the Medical Microbiology and Infection Control Department of the Amsterdam UMC, location VUmc. The test showed that in 9 out of 9 tests the prototypes were inserted into the uterus without contamination. In 8 out of 9 tests the prototypes were able to deliver a non-contaminated sample. The test proved that the idea has the potential to take a non-contaminated sample.

The graduation assignment focused on the relation of the uterine microbiome to (sub)fertility. Several potential use cases could benefit from the sampling technique developed in this project. Use cases include improving the pregnancy success rate of subfertile women; increasing the success rate of ART; detection and treatment of other gynaecological disorders; and sampling other microbiomes outside the gynaecological field. Depending on the findings of gynaecological research with the sampler, the use case can be further specified.

The prototype prompted important discussions between key stakeholders with regards to improving the sampling technique and research into the relation between the uterine microbiome and (sub)fertility. Follow-up studies are needed with a sampler specifically designed for research purpose. This sampler should be designed on a scale of 1:1 for in vivo tests. The goal of these tests would be to determine the relation between the uterine microbiome and (sub)fertility. Based on these results, the use case should be further defined to be able to design a sampler for commercial use. A commercial product is currently not available but could be in the future, given that the prototype has shown the potential to take a non-contaminated sample.

Project recommendations

Different developments are required before this concept can become a reality and be implemented in hospitals. Figure 75 shows the various steps that can be taken to realise the proof of principle and what steps could be taken to develop a research sampler and a commercial sampler. In the overview, a linear process has been illustrated. In real life, it would be a more iterative process. Important transitions for the continuation of the project have been marked.

For fundamental research into the uterine microbiome, a device is needed that can take non-contaminated samples. Funding is needed in order to make this possible. This funding is required for design and prototyping of a device that could be tested on, for example, 100 patients. For this prototype, the recommendations from the test and the Risk Analysis should be taken along. The research sampler could be developed as a collaboration between IQ Medical Ventures and UMC Utrecht. The results of Next-Generation Sequencing need to show if and how the uterine microbiome is linked to (sub)fertility or other gynaecological disorders.

Depending on the results, a use case for a commercial sampler can be developed. This product should be more focused on the usability for the gynaecologist, being producible in larger batch sizes and being profitable for a company. This commercial sampler needs to be designed, prototyped and tested before it can become available for hospitals. The recommendations of the test should be taken along. A more extensive Risk Analysis will also result in additional product recommendations. If the transition to a commercialised sampler becomes viable after further research, IQ Medical Ventures could market it as a new product.

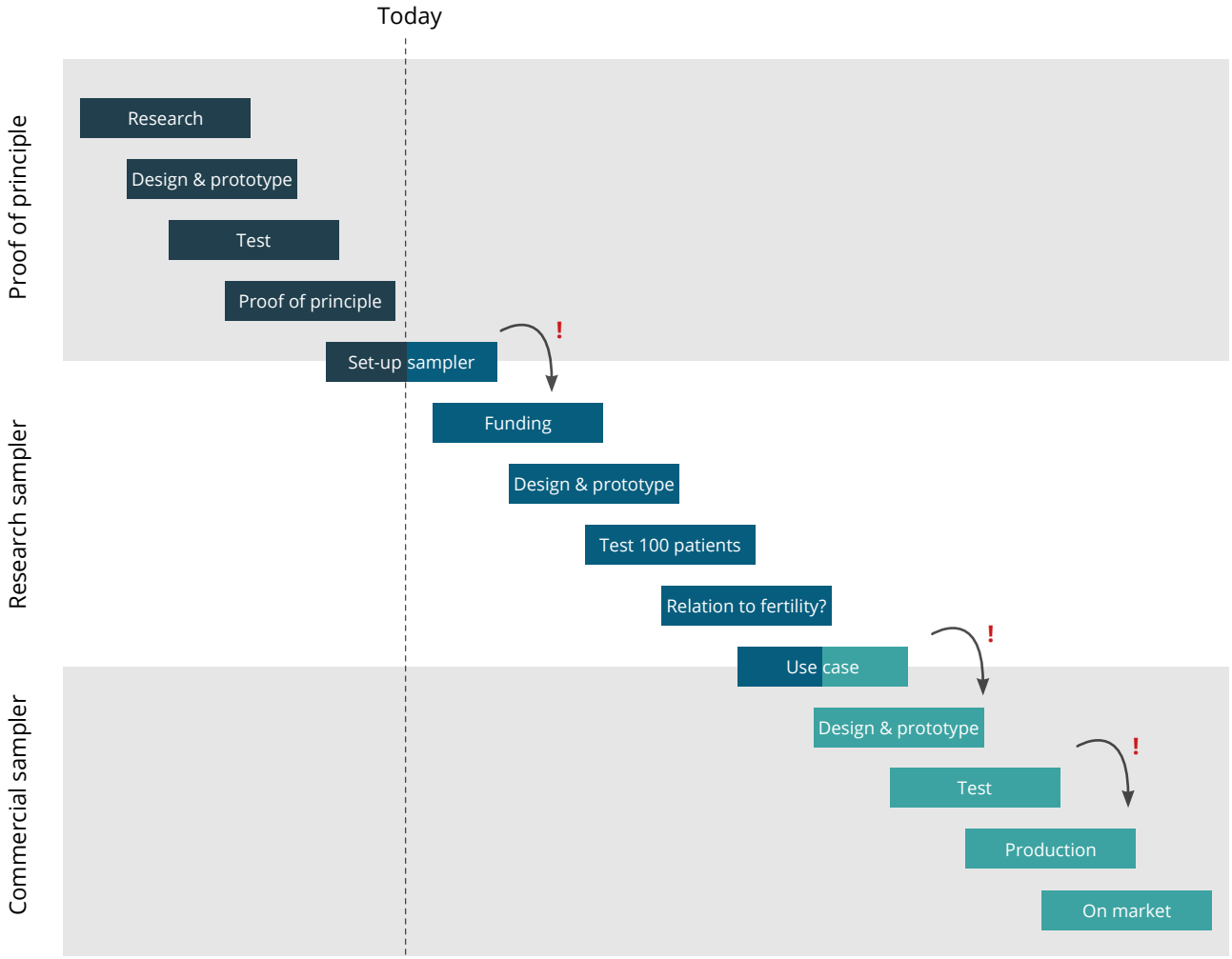


Figure 75: Project recommendation scheme

Evaluation

I learned a lot when diving into the world of product development for microbiology in gynaecology. During the project, I felt like a spider in a web between the specialisations. First, I started with observations and began to understand the field of subfertility and gynaecological procedures. Second, as a designer I had to translate these findings and requirements into a suitable solution. Third, I had to make a prototype and a set up for a microbiological test, an entirely new field to me. Finally, at IQ Medical Ventures I was able to see the different stages of medical product development and the steps involved with bringing it to market. The combination of these various fields and design activities made me eager to learn more, do more and deliver more. The enthusiasm of all parties involved encouraged me to stay enthusiastic and focused as well.

During the project, I was able to stay quite on track with the planning. At the beginning of the project, the supervisors helped me to re-evaluate the initial planning. From then I focused on a proof of principle instead of wanting to do too much and ending up with just nothing. During the process, it was sometimes hard to stay critical to my work. I was working alone during the graduation and had to find the right experts at the right time for the right feedback.

I loved working on most of the learning goals that were set at the beginning of the graduation project. During the collaboration with the different disciplines, I had to become an expert in designing with and for medical professionals. Thanks to Mark Hans Emanuel I was able to conduct user research in the hospital context, which helped me to better understand the context. Improving my graphical communication helped in communicating my ideas to everyone involved in the project, especially when discussing the test with the microbiologist. In this phase, prototyping for a realistic 'offline' test was important. By first prototyping to evaluate the concepts, I was able to make a suitable prototype (Figure 76) for a test to prove the principle of the sampling technique. Because I focused on a proof of principle, I did not specifically focus on the materialisation of medical products.

In the future, I hope to apply the skills learned during this project in a multidisciplinary team to contribute to the improvement of people's lives in a medical context.

Conclusion

This graduation project delivered a proof of principle for a non-contaminated sampling technique. The project should first be developed further as a research sampler to provide evidence for a use case. If there is evidence for a suitable use case, a more commercialised sampler can be realised. As a graduate student, I can look back on an inspiring project in which I accomplished many of my learning goals.

Figure 76: Enjoying the project to even the smallest detail

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