

Product Development Cycle of a Surgical Device for Mitral Valve Repair
and
Surgical Training Simulator Development Plan for the Same

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Dedication

To Mom, Dad [1], Gaura, and Binx

– for unconditional love and support.

Abstract

Mitral Valve Regurgitation (MR) is a disease in which the valve leaflets fail to fully coapt (close together) allowing blood to flow in the reverse direction. If left untreated, MR progression can lead to serious heart problems including atrial fibrillation and congestive heart failure.

A study of the Society of Thoracic Surgeons Adult Cardiac Surgery Database for the eight year period spanning 2000-2007 found that 47,126 operations were performed for isolated MR alone [2] with an increase of the surgical valve repair rate (versus total valve replacement) from 51% to 69% in the same time interval [2][3].

The NeoChord DS1000 is a novel surgical instrument that facilitates mitral valve repair for MR on a beating heart. As the demand for further instrumentation for beating heart mitral valve surgery grows, so too will the demand for mitral valve surgical training simulators. There exists an unmet need for such a simulator that incorporates the beating heart, anatomically correct heart anatomy and leaflet motion, physiologically correct flow rates, and the ability to interface with surgical devices.

The objective of this thesis is to 1) describe the product development cycle for the DS1000, a surgical instrument for Mitral Valve repair. A chapter is then provided for 2) adapting the device development cycle to a development cycle for a simulator. This is followed by 3) a chapter of cardiac related simulators currently on the market as well as examples of how these simulators were validated. This thesis concludes by 5) combining the knowledge of the first four chapters to describe a development plan for a surgical training simulator for the beating mitral heart valve.

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List of Abbreviations

CAD – Computer Aided Design

CHA – Clinical Hazards Assessment

DAT – Design Analysis Testing

DVT – Design Verification Testing or Design Validation Testing

EN – European Standards

ePTFE – Expanded Polytetrafluoroethylene

FDA – Food and Drug Administration

FMEA – Failure Modes and Effects Assessment

FMECA – Failure Modes, Effects, and Criticality Assessment

IFU – Instructions For Use

ISO – International Organization for Standardization

LA – Left Atrium of the heart

LV – Left Ventricle of the heart

LVAD – Left Ventricular Assist Device

MR – Mitral Valve Regurgitation

MV – Mitral Valve of the heart

PCT – Patent Cooperation Treaty (also called an international patent application or a non-provisional patent application)

RA – Right Atrium of the heart

RV – Right Ventricle of the heart

SUT – Simulated Use Testing

SyRS – System Requirements Specifications

V & V – Verification and Validation

CHAPTER 1- BACKGROUND

1.1 Introduction

Mitral Valve Regurgitation (MR) is a disease in which the valve leaflets fail to fully close together (coapt). Blood then flows in the reverse direction, regurgitating back into the Left Atrium. If left untreated, MR progression can lead to serious heart problems including atrial fibrillation and congestive heart failure.

From a sample population study it was estimated that 1.7% of the United States population has some form of MR [4]. Per the year 2000 Census data, that amounts to approximately 3.5 million individuals. Approximately 250,000 patients are actually diagnosed each year [5].

A study of the Society of Thoracic Surgeons Adult Cardiac Surgery Database for the eight year period spanning 2000-2007 found that 47,126 operations were performed for isolated MR alone [2]. Additionally, the preference in those operations has shifted further to surgeries repairing the native valve (as opposed to complete valve replacement). The surgical repair rate increased from 51% to 69% [2][3]. This percentage was similar in a study of the European population [6].

The current operation to correct this ailment is an invasive procedure in which the chest is opened and the heart is placed on by-pass. The development of new surgical devices has allowed for a shift towards less invasive procedures performed on the beating heart. This shift also increases the need for the development of surgical training simulators specifically for beating heart valve procedures.

This thesis describes the product development cycle for one of these new surgical devices, the NeoChord DS1000. An example is then provided for adapting the device development cycle to a simulator development cycle. This is followed by examples of cardiac related simulators currently on the market as well as examples of how these simulators were validated. In its final objective, this thesis concludes by combining the knowledge in the first four chapters to describe a development plan for a surgical training simulator for the beating mitral heart valve.

1.1.1 Mitral Valve Regurgitation

The heart contains four chambers: Right Atrium (RA), Right Ventricle (RV), Left Atrium (LA), and Left Ventricle (LV) (Figure 1). Unoxygenated blood returns from the body, via the inferior and superior vena cava and collects in the RA. Blood is then passed into the RV which, upon contraction, sends blood to the lungs to become oxygenated. The oxygenated blood returns to the heart collecting in the LA. The Mitral Valve (MV) of the heart separates the LA from the LV. The force from the contraction of the LV propels oxygenated blood throughout the entire body.

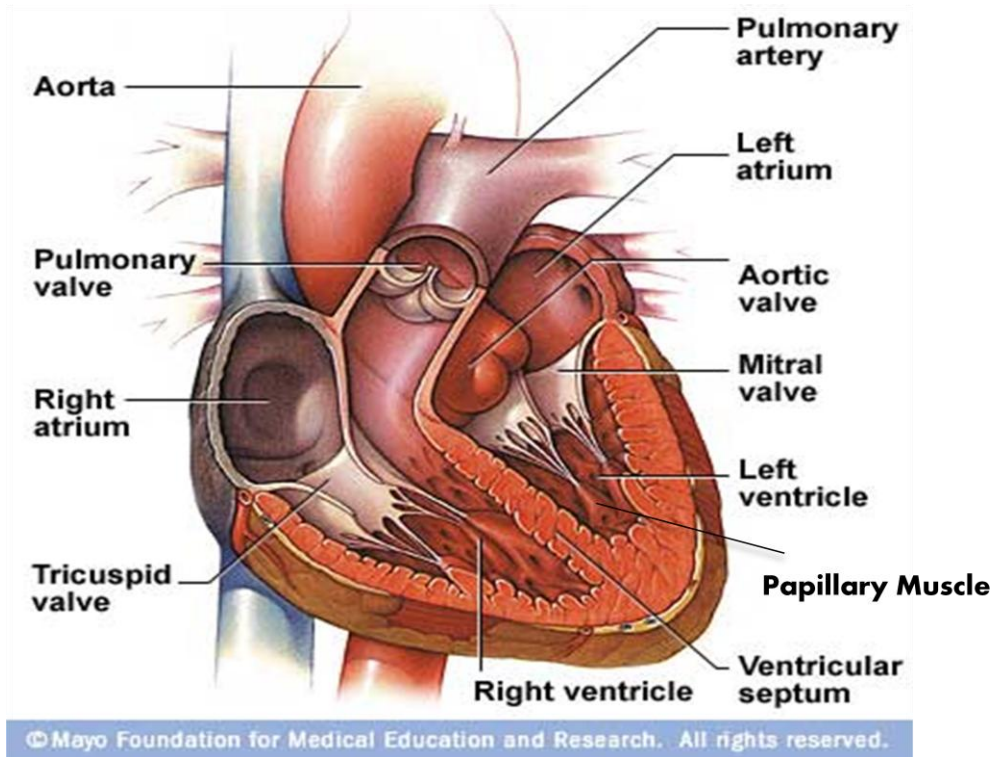


Figure 1: Heart Anatomy [7].

Reference [8] for a well illustrated introduction to the anatomy of the Mitral Valve.

Briefly, the MV is comprised of two leaflets and several chordae tendinae, all of which act to create a one-way valve allowing blood to flow in only one direction while in the heart (Figure 2). The two leaflets coapt during LV contraction (systole) and create a seal preventing blood from flowing backwards (regurgitating) into the LA. The chordae tendinae further assist the leaflets in resisting the back pressure of the blood during systole.

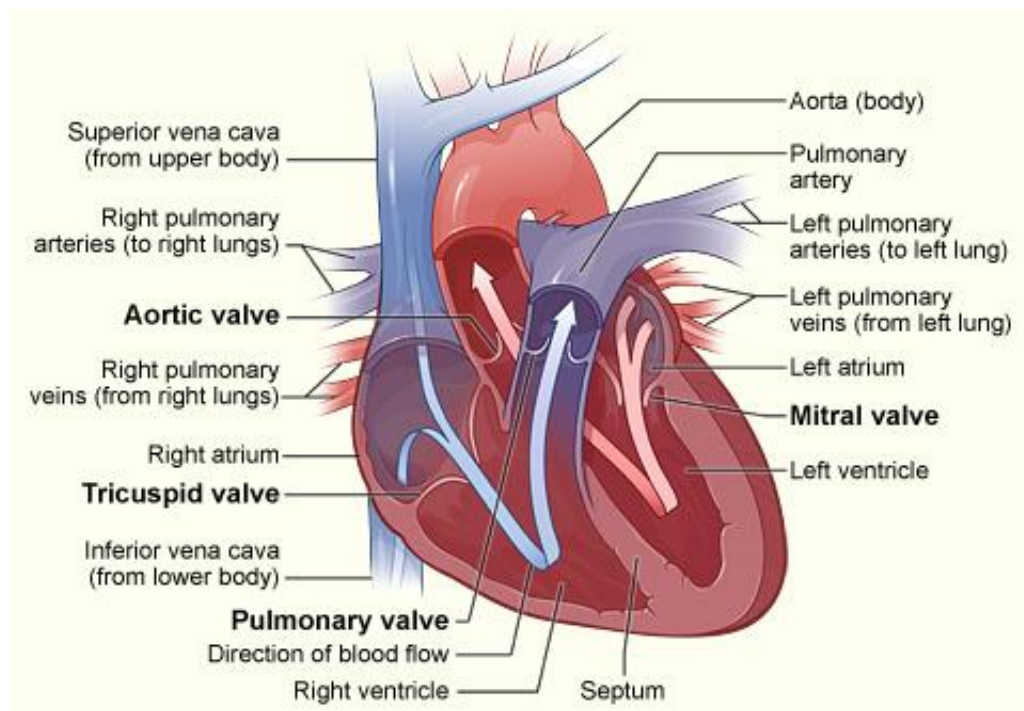


Figure 2: Direction of Blood Flow [9].

For a variety of reasons (disease, broken tendinae, aging, degradation, calcification, etc.) the MV can fail to fully prevent blood regurgitating back into the LA. This occurrence is commonly referred to as Mitral Valve Regurgitation (MR). In mild cases, the two leaflets do not have complete coaptation. In severe cases, one or both leaflets invert and flap backwards into the LA, a condition called valve prolapse (Figure 3).

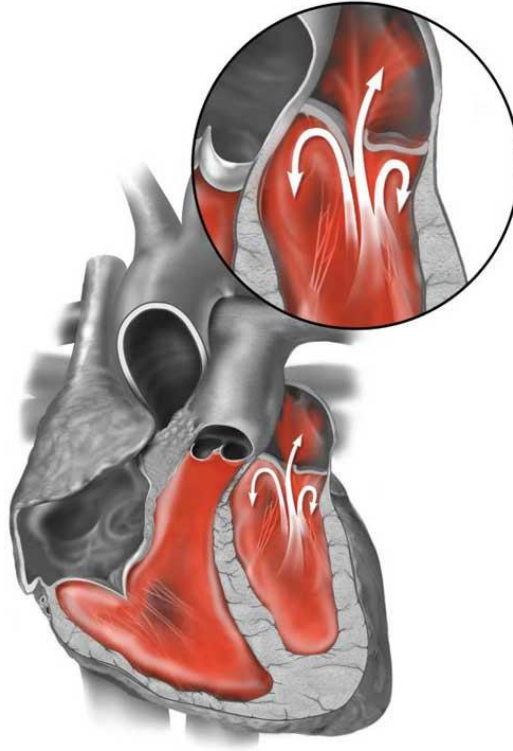


Figure 3: Prolapsed Mitral Valve [10].

Pathways leading to MR are numerous. Two mechanical causes are annular dilation and papillary muscle displacement. The annulus (or annulus fibrosus as labeled in Figure 4) is the anchor point for the leaflets and defines the circumferential orifice size of the valve. “Annular dilation causes MR by increasing the orifice area and decreasing the [leaflet] coaptation length” [11]. Figure 1 shows that the chordae tendinae connect the MV leaflets to the papillary muscle. Papillary muscle displacement pulls the leaflets further into the ventricle preventing proper leaflet coaptation and thereby causes MR.

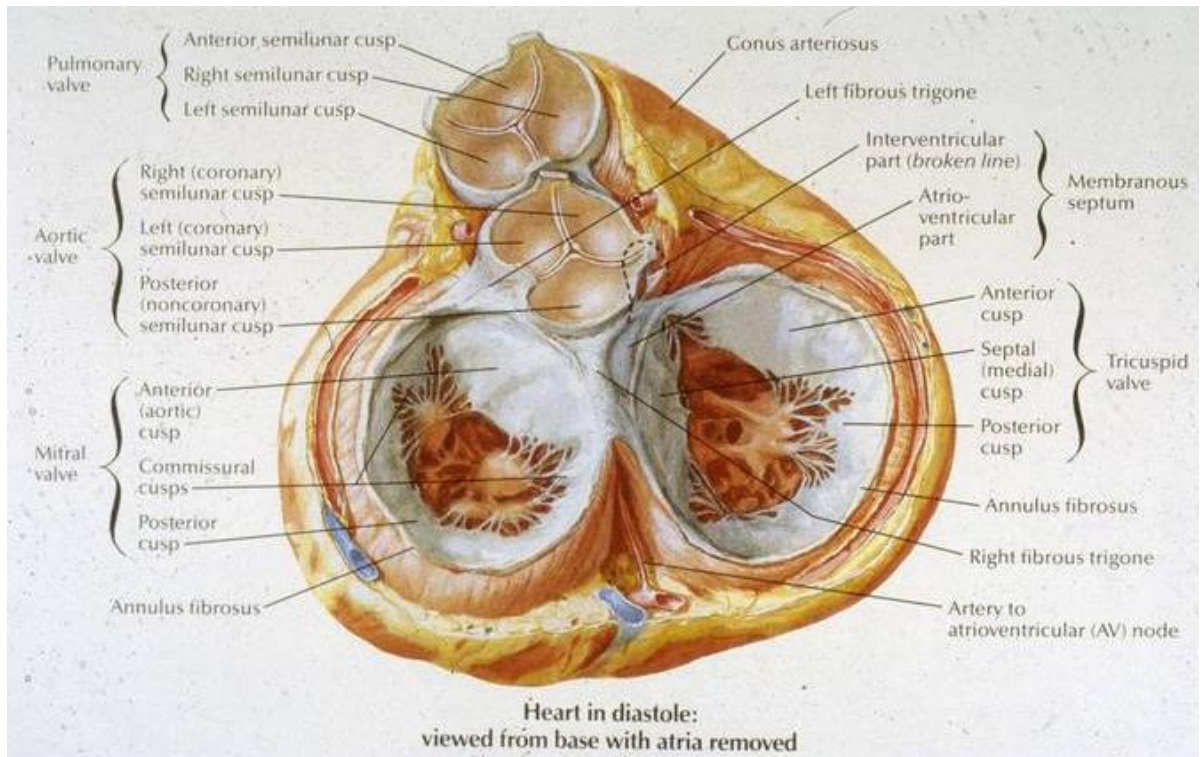


Figure 4: Cross sectional view of the heart in diastole [12].

Two disease pathways causing MR are fibroelastic deficiency and Barlow’s disease. With fibroelastic deficiency, patients lack sufficient connective tissue. This causes thinning of the leaflets and chordae tendinae which leads to eventual chordae rupture. The chordae rupture and subsequent leaflet prolapse is often in an isolated area [13]. It is suggested that “a process of gradual disorganization of [the] collagenous core related to aging” occurs where in the highly structured connective tissue of the chordae elongate and eventually become random [14].

In contrast, the myxoid degeneration associated with Barlow’s disease includes leaflet thickening, large redundant leaflets, chordae tendinae elongation/rupture, and annular dilatation [15]. The entire valve is often affected.

For the more curious reader, Pedrazzini [5] provides further details of MR, its causes, mechanisms, classifications, assessment, and treatments. Malkowski [16] provides further details regarding anatomical dimensional differences between healthy and diseased valves (leaflet thicknesses, chordae tendinae length, annulus diameter, etc.). Atalay [17] provides similar details for a younger patient population (approximate mean age of 12 years old). Millington-Sanders [14] provides details of the structure and composition of the chordae tendinae using scanning electron and light microscopy. Zoghbi [18] classifies MR into mild, moderate, and severe categories. Parameters include heart chamber size, leaflet thickness, Doppler parameters based on blood flow, regurgitant volume and fraction, and effective regurgitant orifice area.

1.1.2 Current Surgical Techniques to Correct Mitral Valve Regurgitation

The current surgical standard to correct MR is very invasive and requires the heart to be placed on bypass. It involves opening the chest cavity via a sternotomy (“cracking open the chest”). The heart is then put on bypass and the LV is cut open. The surgeon implants artificial chordae tendinae (ePTFE suture). The length of the artificial chordae is estimated based on the length of the intact native chordae tendinae. The artificial chordae are then passed through the leaflets and anchored to the papillary muscle with the native chordae (Figure 1). Since the heart is not pumping, the tension of the artificial chordae must also be estimated. Additional steps may be taken such as resection of the leaflet (cutting a section of the leaflet out and stitching it together resulting in a smaller leaflet) or implanting an annular ring (a ring placed around the circumference of the MV used to decrease the MV’s diameter (Figure 4)).

The Alfieri stitch (or Edge-to-Edge repair) is an alternative to anchoring suture to the papillary muscle. A few stitches are placed through the prolapsing segment of the flailing leaflet and the corresponding point on the normal leaflet connecting the two at a single point at their free edges (Figure 5). This results in a mitral valve that is connected in the middle (correcting the prolapse) creating a “double orifice”.

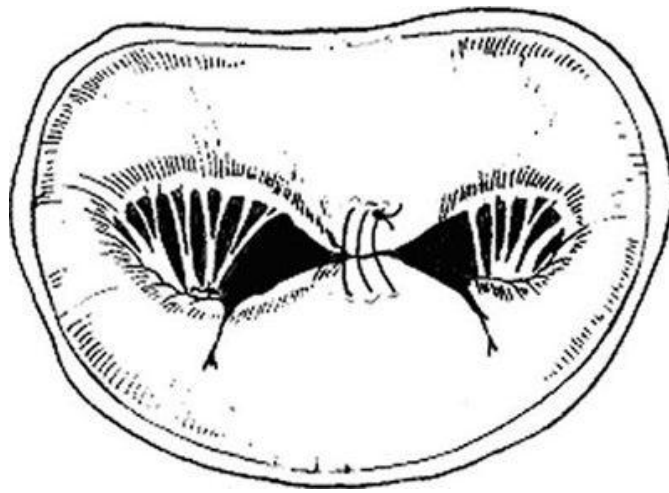


Figure 5: Alfieri stitch (or Edge-to-Edge repair) [19].

After the corrections are in place, the heart is taken off of bypass, restarted, and all incisions are closed. The average operation time is 3-4 hours and the patient remains monitored in the hospital for 4-6 days.

An alternative approach to the open heart surgery is to use the robotic DaVinci® system. The system allows for a much less invasive approach to gain access to the MV, however, since the system is not approved for surgery on the beating heart, bypass is still required. Falk [20] provides a summarized step-by-step description of a mitral valve surgery using

the DaVinci® system and also describes the ZEUS system. Kypson [21] then describes the AESOP 3000 system.

Another alternative is the implantation of an annuloplasty ring. This can be performed on a beating heart. The ring is implanted circumferentially around the mitral valve's annulus (the opening of the valve (Figure 4)). The ring is then tightened, thereby reducing the diameter of the MV annulus and bringing the leaflets closer together. This procedure is more applicable if, through degeneration, the heart has dilated. It is less effective to correct prolapse since it does not directly restrain a flapping leaflet. Examples of annular reshaping products include the Percutaneous Septal Sinus Shortening device by Ample Medical, the BACE by Mardil, and the system by Mitralign [22].

1.1.3 The NeoChord DS1000

The DS1000 is a surgical device created to correct MV regurgitation and valve prolapse, by restraining flailing leaflets, while the heart remains beating (US Patent Pub. No. US 2009/0105751 A1). Access to the heart is gained through a throacotomy (an incision between the ribs). A second incision is made at the apex of the heart (ventriculotomy) and the device is inserted into the Left Ventricle (Figure 6).

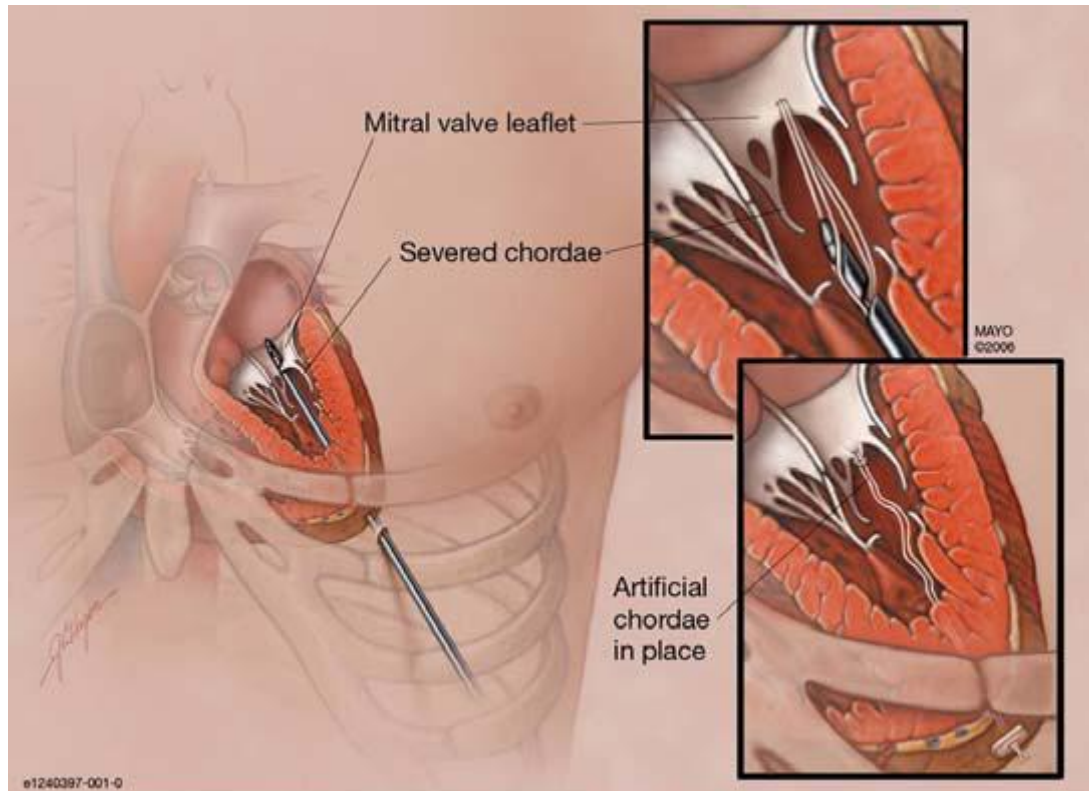


Figure 6: NeoChord DS1000 access via thoracotomy and ventriculotomy [23].

The leaflet is captured with the jaws of the device and integrated fiber optics are used to indicate full or partial leaflet capture. An artificial chordae tendinae (ePTFE suture) is passed through the leaflet, the device is taken out of the heart, and the suture is removed from the device leaving the free ends of the suture in the surgeon's hands. The surgeon creates and passes a knot up to the leaflet. The heart is not on bypass and therefore still beating. Using imaging techniques such as transesophageal echocardiography (TEE), leaflet coaptation and blood regurgitation can be visualized in real-time. Thus, the surgeon can tension the suture as needed until regurgitation is minimized. The suture is then anchored to the apex of the heart. Multiple sutures can be placed when necessary. At

the start of the European Clinical Trial the operation time averaged 2 hours and patients remain monitored in the hospital for approximately 7 days.

Other surgical devices exist that allow delivery of sutures. Examples include the Superstich™ device and the Gore® suture passer; however, none of these are designed for use on the beating heart.

1.1.4 Mitral Valve Surgical Training Simulator

As previously noted, there is a shift in the surgical treatment of MR. The shift is from the highly invasive operation with the heart on bypass to minimally invasive procedures on the beating heart. The NeoChord DS1000 is one of a growing number of options that accomplish this. Another is Abbott's MitraClip (acquired from Evalve, Inc.).

As less invasive beating heart technologies expand, so does the need for a surgical training simulator. An effective simulator must include (among other things) moving and prolapsing Mitral Valve leaflets, correct physiological dimensions, and accurate fluid flow rates and pressures. Finally, the simulator must be validated proving that improvement (learning) gained from using the simulator correlates to improvement performing the actual surgical procedure.

1.2 Objective

First, the generic product development cycle will be described coupled with specific examples from the development of the DS1000 device.

Second, an example will be presented describing how the product (device) development cycle can be adapted to develop a surgical training simulator.

Third, literature research relevant for concept generation and system requirements generation for a surgical training simulator is summarized. The research first describes current validated simulators followed by examples of validation methods. Then current cardiac-related simulator examples are provided. In addition, examples of existing beating heart models are described.

Finally, the three previous sections are linked together to describe the current status and future plan to develop a surgical simulator for Mitral Valve Regurgitation surgery.

NeoChord's funding for a simulator was shifted to the DS1000 device development.

Therefore, the research presented here will be essential during the very initial phase of the NeoChord Mitral Valve Simulator development cycle, and the development cycles presented can act as the overall Project Plan when funds become available to further pursue the simulator.

CHAPTER 2- THE PRODUCT DEVELOPMENT CYCLE

This section describes the generic product development cycle and is coupled with specific examples from the development of the DS1000 device.

The product development cycle is the term encompassing all the stages that an idea goes through on its way to becoming an actual product. Stages vary from product to product, but in general they include concept generation, system requirement specifications, consideration of industry Regulations, design, risk analysis of the design, design analysis testing, and verification and validation testing (Figure 7).

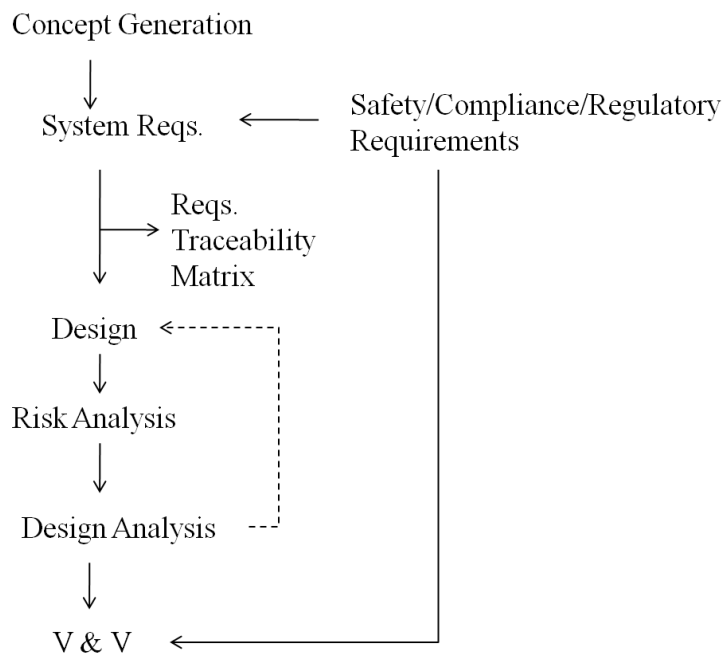


Figure 7: The Product Development Cycle.

The following sections expand on each of the stages outlined above. Each general description is followed by the specific example in the case of the DS1000 (Figure 8).

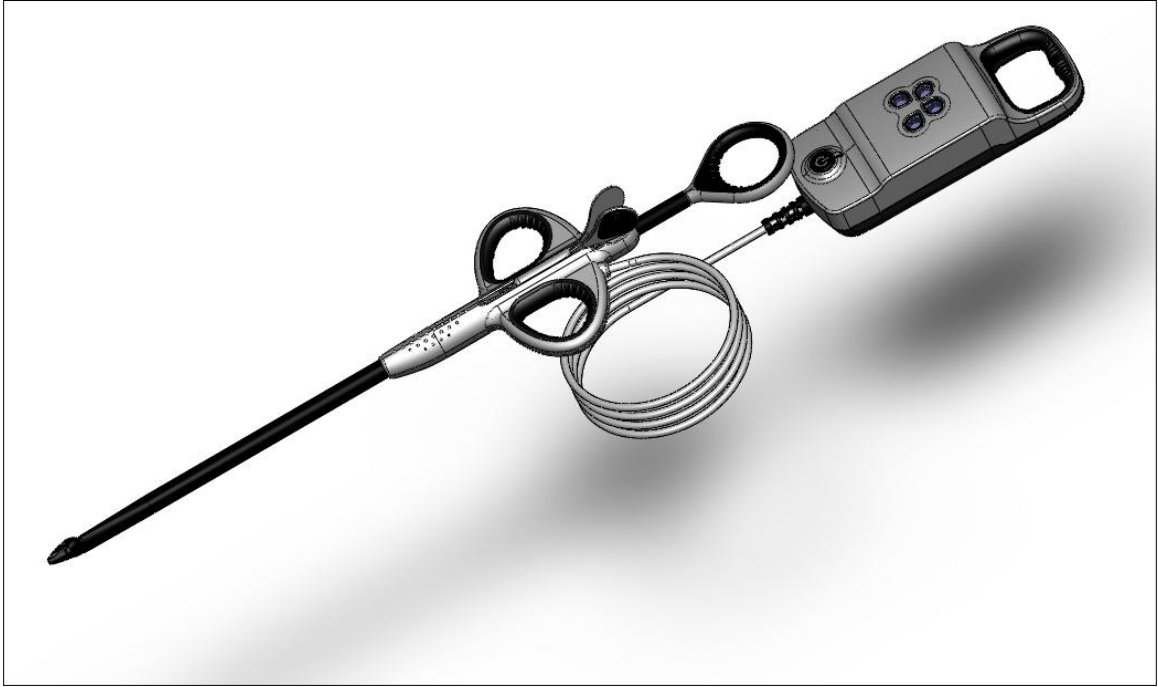


Figure 8: The NeoChord DS1000.

2.1 Concept Generation

In General

The concept generation step is the traditional start of the product development cycle (Figure 7). Its form can range from a formal (possibly extravagant) kickoff to a simple random thought had in the shower.

It is the ideation stage and much of it is intangible. An alternative way to perform a task, an alternative feature, a new function, or a completely new process - this stage stems from a desire to improve the current way things are done.

The freshly conceived idea is further developed. Theoretical investigation, patent searches, initial prototypes, and financial feasibility studies are examples of tools used to bolster support for the new idea.

In product development, this stage traditionally includes patent filing and other efforts to protect the fresh intellectual property. A successful proof-of-concept often concludes the concept generation stage and the transition to a full project hopefully follows.

For the NeoChord DS1000

The majority of concept generation for the DS1000 took place at the Mayo Clinic in Rochester, Minnesota from 2002-2006. The concept was primarily conceived and developed by Mayo's cardiac surgeons Dr. Giovanni Speziali and Dr. Richard Daly and cardiologist Dr. Charles Bruce (US Patent Pub. No. US 2008/0188873 A1).

The concept came from a desire to find a less invasive way to treat MR (section 1.1.2). When the MV fails to properly coapt, it allows blood regurgitation into the LA. The current standard of treatment is open-heart surgery which is a very invasive procedure lasting an average of three hours and resulting in months of recovery.

The Mayo Clinic's concept provided the ability to capture the non-coapting or flailing valve leaflet, deploy in it a suture and tension until proper coaptation is achieved and regurgitation is eliminated. All this was achieved with two relatively small incisions, one between the ribs and the other at the apex of the heart.

Mayo Clinic refined the concept through learning with prototyping and animal studies. One international patent application (also called a non-provisional patent or Patent Cooperation Treaty (PCT)) and one provisional patent application were filed in 2005. The device, used as a custom instrument approved by the Mayo Clinic Institutional Review Board, was eventually used on three patients.

In 2007 the technology license to this device was acquired by NeoChord, Inc. (Minnetonka, Minnesota). As detailed later, the Mayo Clinic device became the starting point for the DS1000 design. NeoChord's design refinements aimed to bring the device to mass production and sales.

2.2 System Requirement Specifications

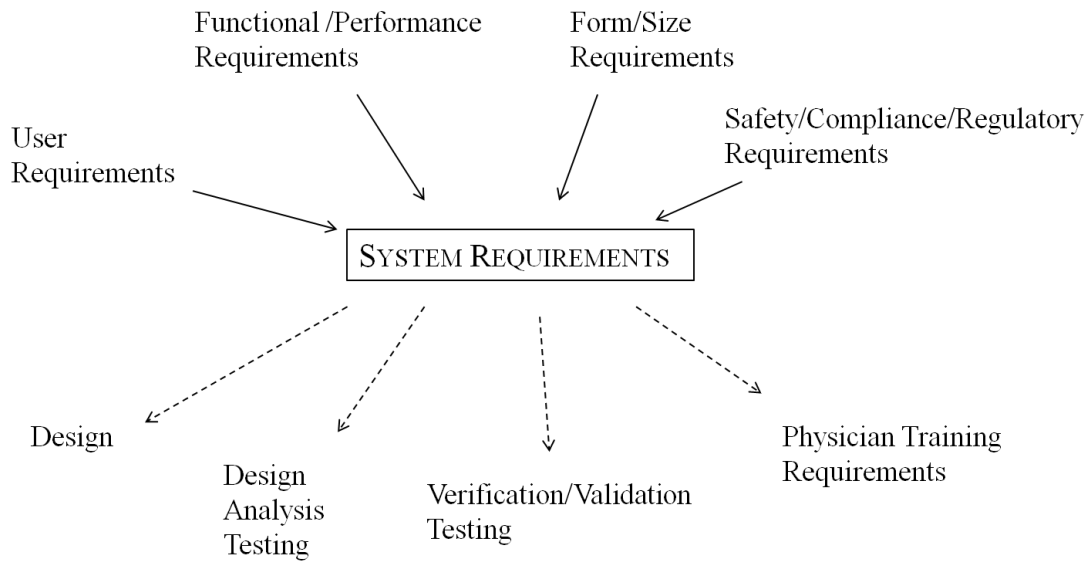


Figure 9: System Requirement's Inputs and Outputs.

In General

Once the product design cycle passes out of the concept generation phase and formally becomes a project, one of the next initial steps is the development of the System Requirements (Figure 7).

These requirements help hone the vision of the new product. Therefore, the requirements describe the product's form, how it will function, what it must be capable of accomplishing, and what it absolutely must avoid doing. Examples of requirement categories include: function, performance, aesthetics, user interface, manufacturability, quality, packaging, labeling, installation, safety, regulatory, and compliance.

Since these requirements will guide the development process, the inputs to the System Requirements are many and varied (Figure 9). The System Requirements guide more than just the design. They will guide the analysis, testing and validation of the product. They can also be used to guide educational materials for the end users (operators).

System Requirements can be refined during the development process just as with the design itself.

For the NeoChord DS1000

The DS1000 device has the following sections in its System Requirements Specifications: Functional, Performance, Environmental, User Interface, and Labeling.

Functional requirements include the use of biocompatible materials, ability to deploy multiple sutures, dimensional limits, ability to capture and not damage the leaflet, and the monitor's battery life (continuous operation).

Performance requirements include percentage of successful first attempt suture capture, suture delivery location on the leaflet, leaflet thickness limitations, ability to withdraw suture, and avoidance of specific medical complications.

Environmental requirements include sterility, packaging, shelf life, and compatibility with operating room fluids (such as saline).

User requirements include adaptability to right- and left-handed surgeons and the ability to operate the suture-capture feature with one hand.

Labeling requirements list the minimum information content displayed on the device, packaging, and Instructions For Use (IFU) (packaging).

A final design consideration was compatibility with imaging modalities. The DS1000 device selected materials that appear distinctly when using echocardiography. Though not directly related to the DS1000, Huang [24], Stoll [25], and Novotny [26] provide useful background on instrument shape, material, coating, and markers used to enhance visualization under different imaging modalities.

2.2.1 Requirements Traceability Matrix

In General

Having System and Design Requirements necessitates two main actions. First, all the requirements for the product must be documented. Second, conformance to all requirements must be proven.

It is highly useful to track, in a central location, all requirements and where conformance was proven.

For the NeoChord DS1000

In the case of the DS1000, this tracking was accomplished by creating a Requirements Traceability Matrix. With a goal of providing a “One Stop Shopping” list, this matrix contained (when applicable):

- All requirements and the documents which contain them.
- The Regulatory Standard that the requirement complies with.
- The Regulatory Bodies that recognize the Standard.
- The Standard that guides the testing of the requirement.
- The corresponding Risk Analysis Severity Level.
- The acceptance criteria rationale.
- The test report documenting testing of, and conformance to, the requirement.

2.3 Regulatory Standards

In General

The Medical Device Industry is closely monitored and heavily regulated. This strict oversight is necessary – people’s lives are at stake. Therefore, general requirements have been established that must be met for any device (when applicable). These take the form of standards for safety, compliance, regulations, and guidance documents. Additionally, the type of application – a 510k versus an Investigational Device Exemption (IDE) – determines the main pathway to marketing the device.

For the NeoChord DS1000

The DS1000 complies with the following main requirements:

- EN 1041 – Information Supplied by the Manufacturer of Medical Devices (Labeling)
- ISO 10993 – Biological Evaluation of Medical Devices (Biocompatibility)
- ISO 11135 – Sterilization of Health Care Products (Sterilization)
- ISO 11607 – Packaging for Terminally Sterilized Medical Devices (Packaging)
- ISO 13485 – Medical Devices – Quality Management Systems (Quality System)
- ISO 14971 – Medical Devices – Application of Risk Management to Medical Devices (Risk Management)
- EN 60601 – Medical Electrical Equipment – General Requirements for Safety

2.4 Design

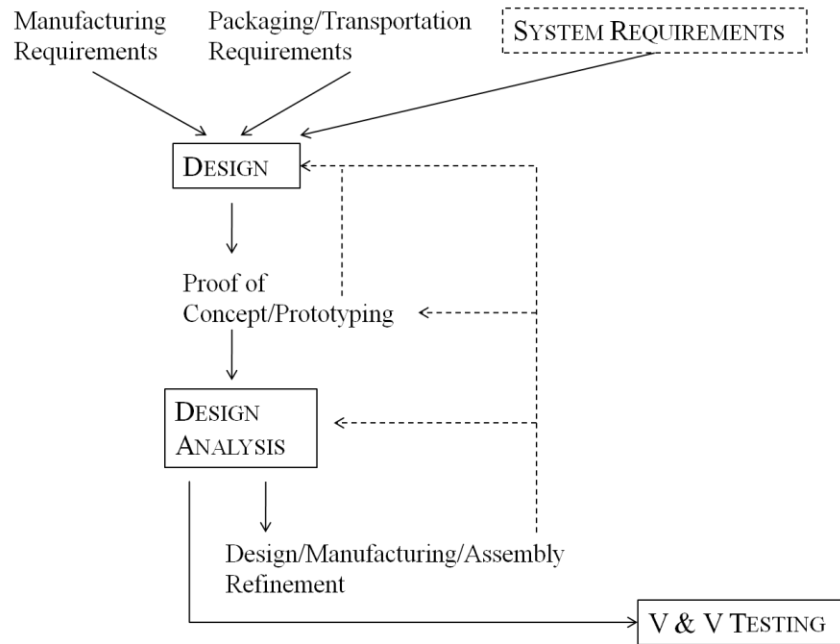


Figure 10: The Design and Design Refinement Cycle.

In General

The Design and Design Refinement (Figure 10) will likely consume the majority of a project's time and resources. Despite the best planning to achieve final results in the first attempt, it is very much an iterative process.

Following the initial design, prototyping and more proof-of-concepts will likely be required. Poor prototypes can result in cycling back to refine the design. Successful prototypes lead to an accepted design. The accepted design will proceed to Design Analysis Testing (detailed in section 2.6).

Findings from the Design Analysis Testing lead to more options. If small modifications are needed, the updated design could repeat Design Analysis Testing. If more drastic changes are needed, another round of design and prototyping refinements could follow. Failures of the Design Analysis Testing could result in drastic design changes. Successful Design Analysis Testing leads to Verification and Validation Testing (detailed in section 2.7).

For the NeoChord DS1000

The initial conception, proof of concepts, prototypes and human trials were completed by physicians at the Mayo Clinic (Rochester, Minnesota (section 2.1)). The technology license was acquired by NeoChord, Inc. (Minnetonka, Minnesota). Worrell Engineering (Minneapolis, Minnesota) completed major design refinements to the physical form and the materials used. Several iterations of the device's form took place based on feedback from experienced cardiovascular surgeons.

After the Design Analysis Testing (detailed in section 2.6), design refinements were made to some bonds, interconnections, and electronic components. These changes made the assemblies more robust. Additional form and fit changes were made to some components for efficient (more accurate and repeatable) manufacturing. The assembly procedure was refined to further reduce foreign material and to ensure flush optical fibers at the tip of the device.

For all of the aforementioned refinements made, each proposed change was assessed for additional risk (detailed in section 2.5), prototyped, and tested prior to official implementation.

2.5 Risk Analysis

In General

The Risk Analysis is equally critical to the design process. All elements of the design, manufacturing/assembly process, and the surgical procedure are assessed for all modes of failure. A multifunctional group (design, engineering, research, manufacturing, quality, regulatory, sales, marketing, surgical experts (end users)) performs a step by step evaluation of anything that could go wrong.

The Clinical Hazards Assessment (CHA) is the “top-down” approach to the failure analysis. It focuses on failures that could occur in the surgical procedure and then feeds into the FMECA.

The Failure Modes and Effects Assessment (FMEA) (or Failure Modes, Effects, and Criticality Assessment (FMECA)) is a “bottom-up” approach to the failure analysis. Based on CHA failures, this focuses on the individual components, then subassemblies, and finally the full device.

These risk assessments reveal the most vulnerable or critical aspects of the surgical procedure and device design. They usually track risk identification, evaluation, control, and residual risk. The results aid in identifying aspects of the design that need refinement,

aspects of the assembly that require additional precautions, and aspects of the surgical procedure for which extra training may be needed.

For the NeoChord DS1000

A Design FMEA was performed for the NeoChord DS1000. A cross-functional design team (representing engineering design, research, manufacturing, quality, and regulatory) assessed the risk for every component, subassembly, and the final device. For each item the failure mode, cause of the failure, effect of the failure, severity, probability of occurrence, and overall risk score were listed. After control measures were established, the probability of occurrence and overall risk score were reassessed. The final conclusion of the mitigated risk fell into one of three categories: Broadly Acceptable, Moderate Risk: Acceptable, and Intolerable.

Broadly Acceptable risk levels are essentially negligible and do not require active risk reduction. Moderate Risk: Acceptable (formerly As Low As Reasonably Practicable) risk levels must be reduced to the lowest level possible that reasonable efforts (including practicality, time, and cost) allow. Intolerable risk levels must be reduced to acceptable levels before use of the product can be allowed.

The Design FMEA identified approximately 75 risks and none had an Intolerable risk level.

A separate Process FMECA was performed for the manufacturing process. A cross-functional manufacturing team (including engineering design, manufacturing, operators,

quality, and regulatory) assessed the same components, subassemblies, and final assembly from a manufacturing standpoint: failure mode, cause, effect, severity, probability, and overall risk based on events that could occur during the manufacturing process. Approximately 120 risks were identified and none had an Intolerable risk after mitigation.

The CHA for the NeoChord DS1000 included assessments by experienced cardiac surgeons, the design engineering group, the manufacturing engineering group, and the manufacturing team. The CHA identified the same items listed previously (failure, cause, effect, etc.). However, the CHA looked at each step of the surgical procedure (rather than each component of the device) and identified risks or surgical complications that could occur. Approximately 45 risks were identified and none had an Intolerable risk.

2.6 Design Analysis Testing

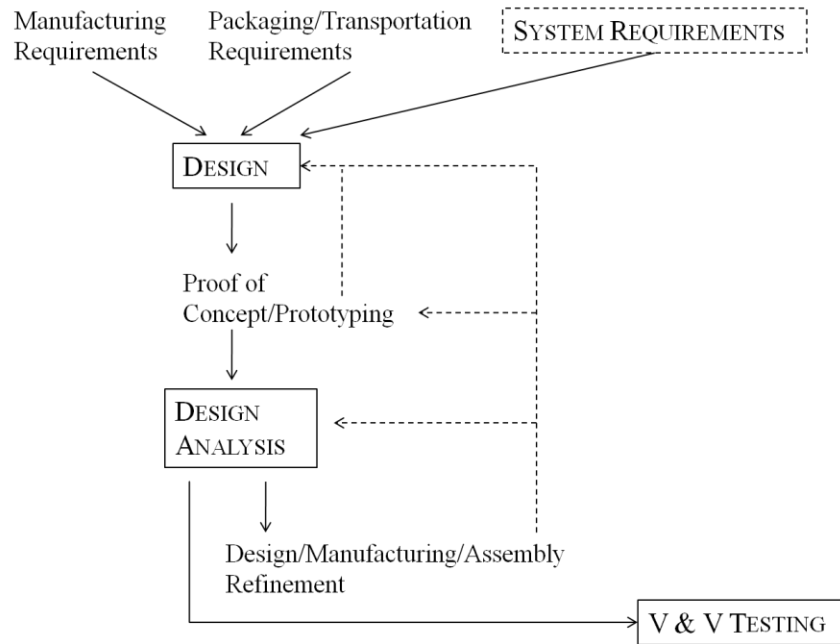


Figure 11: The Design and Design Refinement Cycle (repeated).

In General

The Design Analysis Testing (DAT), or feasibility testing, encompasses all studies performed to understand and quantify the design's attributes.

DATs can be performed for a variety of reasons:

- To establish a baseline understanding of the attributes of the initial design (e.g. bond strengths).
- To compare design alternatives.
- To study the effects of design, manufacturing, or assembly process changes.
- To troubleshoot issues.

- To determine limits, ranges, and tolerances bounding the design (e.g. for size, motion, mass, etc.).

DATs can be both formal and informal tests. Examples include:

- Physical tests of components, subassemblies, or the full system.
- Computer aided design (CAD) analysis.
- Subjective evaluations assessing visual, tactile, audible, olfactory, and gustatory qualities.
- Testing to a requirement or to ultimate failure.
- Assessing manufacturing and assembly refinements.
- Assessing performance in a traditional animal or cadaver model.

For the NeoChord DS1000

For the development of the DS1000, formal design analysis testing (DAT) was performed in the following areas: mechanical, electrical, and simulated use.

Mechanical -

Mechanical Design Analysis Tests were used to 1) confirm that the design could meet its load requirements, 2) quantify failure loads, and 3) assess different bonding options.

Mechanical testing was performed to assess structural integrity of the system. Joints, interconnections, and bonds were stressed in a fashion similar to what will be

experienced during use in surgery. Loads were first applied incrementally to the desired requirement. The load requirements were derived from loads expected during use in surgery and incorporate safety factors where appropriate. If the interconnection under test met the load requirement or if there was no established requirement, increasing load was applied until failure occurred.

Electrical -

Electrical Design Analysis Tests were performed to assess 1) the optical display monitor's operation lifespan, 2) the battery temperature during use, 3) electrical safety per accepted Standards (EN 60601), and 4) anomalies relating to unexpected failures (both turning on and off).

Simulated Use -

Simulated Use Design Analysis Testing was performed to 1) assess the system's ability to capture a mitral valve leaflet 2) without causing damage, 3) capture and retract suture in the first attempt, 4) operate successfully on the leaflet thicknesses required, and 5) operate effectively with the suture sizes permitted. Additionally, evaluations of various suture retention mechanisms and surgical techniques were assessed.

Refinements -

On several occasions, the clinical performance was assessed on a traditional porcine model. More impromptu, informal testing (which may also be referred to as engineering analysis or evaluations) was performed throughout the product development cycle.

Reasons included evaluating different component configurations, defining tolerances and limits, and investigating failures.

Design Configuration Tracking

Since Design Analysis Testing occurs during the design refinement process, a Configuration Tracking Matrix was created for the DS1000. It tracks the revision level of all components and assembly methods used to construct the device, as well as what testing each configuration was used in. As design changes occur, this matrix allows one to assess if the testing on older revisions remains valid, or if the changes warrant repeating of testing.

2.7 Verification and Validation Testing

In General

The Verification and Validation Testing (V&V Testing) encompasses the set of tests that prove the device meets the stated design requirements. The FDA has adopted the ISO 8402:1994 definition of verification and validation. “Verification is confirmation by examination and provisions of objective evidence that specified requirements for a

particular device or activity at hand have been met.” “Validation is a step beyond verification to ensure the user needs and intended uses can be fulfilled on a consistent basis.” In other words, verification uses objective metrics to ensure the device meets the design specifications. An example would be to confirm the length dimension of the device. Validation confirms that the device consistently performs as intended. An example would be to confirm the ability to capture suture.

For the NeoChord DS1000

For the DS1000, the Verification tests included the Mechanical and Electrical Design Verification Tests. They assessed objective metrics including dimensions, load strengths, mass, travel distances, voltage, and operating time.

The Validation tests included the Simulated Use Design Validation Test. It assessed performance requirements including the ability of an instrument to exchange multiple cartridges, capture and not damage the leaflet, visually indicate proper leaflet capture, and consistently deploy multiple sutures of multiple sizes.

Additionally, Validation testing was performed for the device’s assembly procedures. The purpose was to assure that acceptable devices are consistently produced when built within the documented parameters.

CHAPTER 3- THE SURGICAL SIMULATOR DEVELOPMENT CYCLE

This section describes how the product development cycle for the DS1000 device can be adapted to develop a surgical training simulator for the DS1000 device/procedure.

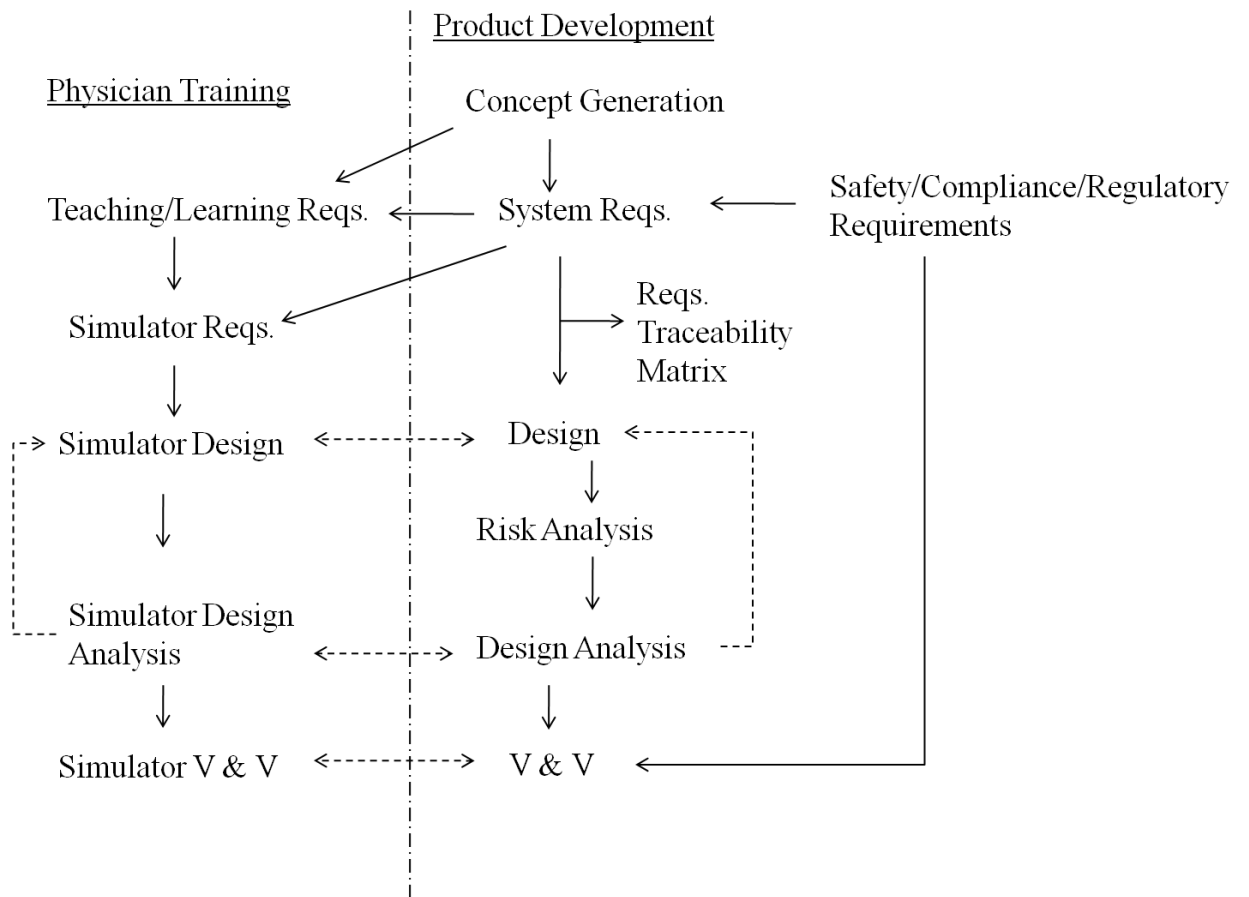


Figure 12: The Surgical Training Simulator Development Cycle extension of the Product Development Cycle (Figure 7).

As depicted in Figure 12, the development of a surgical simulator (or a full physician training curriculum) can be done in parallel and in complement to the product (surgical device) development cycle.

The product concept and system requirements can feed into the simulator's requirements. A product can be novel in both its design as well as its surgical technique. Therefore the simulator's teaching/learning goals must also reflect this. Accordingly, these teaching/learning goals feed into the simulator's design requirements (which are analogous to a product's system requirements).

The design phases for both the product and simulator contain an interesting interplay. If one, either the product or the simulator, is established, robust, and validated, then the other can be tested against it. For example, against a validated simulator, the product can repeatedly be tested, refined, and re-tested. The opposite is also true – having an established product allows the simulator to be refined until it accurately mimics the product's environment of use.

Additionally, if designed in parallel (the simulator and product (device) are designed with each other in mind), the following interplay can be found. The design of the product can influence the design of the simulator. Initially, the intended use of the product defines what the simulator must mimic. The critical aspects of the product's intended use also influences the critical aspects of the simulator. Complimentary, the design of the simulator influences that of the product. As the simulator design becomes more tangible, it can indicate shortcomings in the product's function. In this cyclic relationship, whether the product is evaluated against the simulator or vice versa, the same two questions can

be posed: 1) Does the product fail to perform or 2) Does the simulator fail to mimic reality? The refinement of one drives refinement of the other.

CHAPTER 4- SURGICAL SIMULATORS

This chapter details existing simulators for surgery. First, the importance and value of simulators is described as it pertains to their roll in surgical training. Next, examples of several types of surgical training simulators are provided to give a sense of the diverse range of surgical procedures currently simulated. That is followed by examples of simulator validation methods. This provides 1) proof that simulators are effective learning tools and 2) examples of how to incorporate the simulator into the full teaching curriculum. This chapter concludes with examples of cardiac-specific surgical training simulators.

4.1 Surgical Training Simulators

4.1.1 Surgical Simulators – The Argument For

“The gold standard for research into clinical questions [and practice of surgical techniques] is to study them in real patients, but barriers to doing this may include risk to patients, the fear of medico-legal repercussions for participants, and the cost when the events of interest are rare and large studies are needed”
[27].

There exist a multitude of rationales supporting the use of simulators for training of surgical procedures. Two of the main drivers are risk and resource limitations. The risk is too great, to the patient and potentially the surgeon, to allow initial practice of a

procedure to take place on a human patient. However, training resources are becoming more and more limited. This theme is further illustrated by the following excerpts.

“As pressures intensify to use Operating Room time and resources efficiently, less time is available for [the] teaching and practice of fundamental technical skills. Ethical concerns about teaching and learning basic surgical techniques on live human patients have been voiced. The movement toward increased specialization in academic teaching hospitals has resulted in more highly complex and challenging surgical problems which demand greater surgical expertise. Technical evolution in surgery has created new skill sets and techniques that must be mastered by both practicing and training surgeons prior to clinical application. Live animals and fresh human cadaver models, considered to be of high-fidelity, are limited by availability, high costs, potential for transmission of infectious disease, and ethical concerns. Lower-fidelity synthetic bench models sacrifice realism for portability, lower costs, and the potential for repetitive use” [28].

“Surgical simulators are undergoing a transition in status from curious novelty, predominantly aimed at attracting attention at surgical equipment exhibits [trade shows, conferences, etc.], to sophisticated instruments for training and assessing surgical skills” [29].

“It has been estimated that a successful operation...is 75% decision making and 25% dexterity. Surgical skills have traditionally been taught through an apprenticeship model, and then subsequently through the rotation residency model

(transferred from Europe by William Halstead). Simulation techniques have been identified as potential methods to reduce risks to both students and patients by allowing training, practice and testing in a protected environment prior to real-world exposure. The need to develop and refine simulation technology for surgical training has been compared with the aviation industry, where simulator use has become a routine tool for training and testing. ... aviators are expected to demonstrate proficiency in a simulated environment prior to participating in commercial flying activity” [29].

In addition to the limits on resources, cost motivations also drive the growing popularity of training simulators.

Accessory costs associated with animal training models include anesthetic, animal care technicians, other disposables (i.e. surgical gloves, sponges, saline solution), and properly equipped facilities. Synthetic trainers do not mandate such accessories. Grober [28] estimates the cost of training per trainee could be 37 times greater with an animal model. Sutherland provides similar themed comments.

“Simulator costs range from \$5,000 for basic laparoscopic simulators to \$200,000 for highly sophisticated anesthesia simulators. Cost of training a surgical resident in the operating room for 4 years was nearly \$50,000” [30].

Factors motivating the use of surgical simulators includes: increasing complexity of operations, constraints on the use of animal models, limitations of available patient material, medicolegal pressures, and fiscal mandates for cost-effective performance” [29].

As a final point, the incorporation of simulators in medical training curricula is growing as more studies show, quantitatively, the effectiveness of simulators as a learning/teaching/evaluation/remediation/certification/training tool.

“The use of simulation in surgical training curricula is becoming more widely accepted, for several reasons. First, [for example in the case of Virtual Reality] VR training has been shown to enhance the acquisition of laparoscopic skills. Second, most simulators are able to provide objective assessment and feedback of the subjects’ performance during the training phase, allowing for continuous skills refinement. Finally, two ... randomized, controlled, double-blinded clinical trials have demonstrated that the operating room performance of subjects receiving VR training is better than that of control subjects” [31].

Simulators can be used for more than practice of the physical motions of a procedure. Simulators can aid in teaching decision making, allow more experience diagnosing different severities/stages of disease progression, and give experience deciding when and when not to operate.

Dankelman [32] further notes that “crisis trainers” could be developed to further train for more stressful, unexpected situations such as instrument failure and poor patient reactions. [32] offers simulators as a means to certify acquisition of a skill and to continuously evaluate retention.

Merry [27] goes further, encouraging simulators to be used for training of the entire surgical team. Surgery is a field “in which teamwork is particularly important. Close communication and coordinated activity between the perfusionist, the anesthetist, the

nursing staff, and the surgeons is essential.” Furthering on the ideas of Dankelman, simulators can offer the surgical team experience dealing with crisis in a safe environment. Simulators can offer the entire surgical team “relevant clinical experience, and it provides opportunities for practice, for feedback, and for reflection” [27].

Kneebone [33] further notes that with simulators, “the training agenda can be determined by the needs of the learner, not the patient, and because the environment is safe, learners have ‘permission to fail’ and learn from such failure in a way that would be unthinkable in a clinical setting. This gives the opportunity to explore the limits of each technique rather than having to remain within the zone of clinical safety.” More knowledge can be gained at the boundaries of the procedure where the limits of the technology can be pushed.

In summary, the need for surgical simulators is growing due to increasing resource limits, needs for experience, and risks. Furthermore, simulators are proving to be effective and more accommodating training tools.

4.1.2 Surgical Simulators - Types

Surgical training simulators are tools to aid in learning and the “assessment of a surgeon’s quality: 1) cognitive skills, 2) technical skills, and 3) social skills” [29].

To this end, surgical simulators can take several forms, each having distinct advantages and disadvantages. For example, “bench [top] models have the advantage of being easy to transport, less expensive than computerized simulators and there is an opportunity to

use the same instruments that are used in the operating room which adds manual familiarity to the training” [34].

Alternatively, Minimally Invasive Surgery “demands psychomotor skills that are not required in conventional surgery, such as hand-eye coordination within a 3-dimensional scene seen on a 2-dimensional monitor. Depending on the type of operation, 15 to 100 procedures are required to reach the plateau of [a] learning curve [reaching an experience level with a low complication rate]” [35].

The diversity of surgical techniques, devices, implants, and training goals results in a great diversity of simulators (and manufacturers).

Aucar [29] provides a brief list of procedures having simulators including tendon transplant, cholecystectomy, limb trauma, hysteroscopy, liver procedures, intravenous procedures, sinus endoscopy, anastomosis, anesthesia, ophthalmology, ultrasound, and arthroscopy.

Additionally, Table 1 is a brief summary of some simulator manufacturers.

Table 1: Examples of Surgical Simulators. Based on Table 1 of [36].

<u>Manufacturer</u>	<u>Simulator</u>	<u>Simulates</u>
GMV	insight ARTHRO VR	Arthroscopy training.
Haptica	ProMIS	Orientation, instrument handling, dissection, suturing, knot tying, and electrocautery.
Immersion Medical	LapSim	Basic laparoscopic skills.
Limbs and Things	Femoro-Peroneal Anastomosis Trainer	Open techniques associated with Femero-Peroneal Anastomosis.
Medical Accessories and Research Corporation	TruSoft Surgical Trainers	Custom soft tissue trainers.
Medical Education Technologies, Inc.	STEP	Basic laparoscopic and procedural skills.
MediSkills Models	Advanced Scope Trainer	Ureteroscopy.
Mentice	MIST-VR	Basic laparoscopic skills.
Reachin Medical	Reachin Laparoscopic Trainer	Basic skills and basic skills with cholecystectomy.
SelectIT	VEST VS One Cho	Basic task training with force feedback, time and performance error measurement.
Symbionix	URO Mentor	Endourologic training.
	PERC Mentor	Percutaneous access procedures.
	GI Mentor	Endoscopy and flexible bronchoscopy.
	Lap Mentor	Basic laparoscopic skills.
SimSurgery	SEP Basic	A variety of basic to advanced laparoscopic skills.
Simulab Corp.	TraumaMan System	Simulated human torso for trauma training courses.
Simulated Surgical Systems	RoSS Robotic Surgical Simulator	Trains physicians to operate the da Vinci robot.
The Chamberlain Group	Robotic Beating Heart Trainer	A complete trainer for off-pump MIS robotic training.
Verefi Technologies, Inc.	EndoTower, RapidFire/SmartTutor	Component skills for laparoscopy.
Xitact SA	Xitact LS 500	Laparoscopy with force-feedback and real-time deformation of organs for clip-cut and dissection.

Lake [36] lays out aspects of an ideal simulation system. Briefly, those aspects include anatomical correctness, use of materials with properties mimicking the actual tissues, accurate haptic (force) feedback, and accurate visual appearance. Lake also notes that an appropriate simulator must also be incorporated into a complete training curriculum since learning is a multidimensional enterprise.

In summary, the number and diversity of surgical procedures currently simulated is growing.

4.1.3 Surgical Simulators – General Validation

The previous section listed many types of simulators. This section discusses how to show that a simulator is effective. “It is not sufficient to show that a trainee’s performance on the simulator improves with practice in that simulator unless the simulator performance correlates with actual operative performance” [37]. In other words, if the simulator does not match reality, measured improvement only shows mastery in use of the simulator itself, nothing more. Validation is the process that links improvement on a simulator to improvement in an actual surgical procedure.

This leads to two basic questions:

- 1) What type or style of simulator works best?
- 2) What aspects of the simulator need to be validated?

To the first question, Sutherland provides a very nice summary of the current state of the surgical simulator field. 30 studies were categorized into four groups based on simulation

type: computer simulator training, video simulator training, physical or model simulator training, and cadaver simulator training. These four groups were compared with no training, standard training, and with each other [30]. Sutherland summarizes which papers compared which training methods and what the outcomes were. The brief conclusion was that any training was better than no training, but there was no clear superior method between the four types of trainers (computer simulator, video simulator, physical simulator, and cadaver).

To the second question, Aucar [29] provides a good summary of the art. The paper summarizes 23 studies categorized by the validity design tested. Internal validity confirms that the simulator works; repeated uses improve performance, regardless of the user's surgical experience level. The simulator is the control in the tests, not the level of experience of the user [29] [30]. External validity confirms that the simulator can distinguish between users' experience levels. Performance on the simulator correlates to the experience level of the user. Finally, construct validity confirms that the simulator accurately represents the actual surgery. The performance on the simulator correlates to performance in the real surgery. It also demonstrates that the simulator measures the skills it is designed to evaluate [30].

Lake [36] provides a different view of these validity concepts. Face validity describes the overall realism of the simulation and confirms the simulator's ability to assess the desired qualities. Content validity describes the simulators realism at the individual component level. Construct validity again shows that the simulator can discriminate between users having unequal skill levels. Concurrent criterion correlates the simulator's performance with an established standard. Tests are first performed on patients and then on the

simulator. McDougall [37] supports using the Objective Structured Assessment of Technical Skills (OSATS). With predictive criterion, tests are performed on the simulator then on the patient to assess the simulator's ability to predict real performance. To these, McDougall [37] adds reliability, the reproducibility and precision of the simulator's results.

In summary, despite the diverse selection currently available, a simulator is an effective training tool only if it is proven to accurately mimic reality.

4.1.4 Surgical Simulators – Methods to Validate

Dankelman [32] notes “the success of ... trainers will depend on the transfer of skills to the operating room....” Previously mentioned were several general validity aspects that should be demonstrated in the development of an effective simulator. But how does one specifically go about demonstrating these? The following provides a few summaries of specific examples.

The Stanbridge [38] paper is discussed in further detail in the next section. Briefly, groups of participants with varying surgical experience were scored on their performance after differing amounts of practice with the simulator. Evaluation metrics included neatness, patency, and time.

To measure reliability, McDougall [37] mentions the following techniques: split halves, interobserver and intraobserver reliability, and test-retest reliability.

Van Sickle [31] demonstrated construct validity of the ProMIS simulator using a laparoscopic suturing task. Subjects were given a latex glove with a series of five paired targets into which to suture. Hand motion analysis was used to measure time, instrument path length/economy of movement, smoothness of movement, and number of errors. Accuracy was quantified by the ability to hit the target with a single suture and safety was assessed by the ability to avoid tears.

Datta's [39] study had two objectives. The first was to establish construct and face validation of a bench simulator. The second was to correlate performance on the bench model with the actual procedure. To the first objective, as subjects performed the task on the simulator, their performance was recorded and retrospectively analyzed by three independent assessors using the OSATS method. To the second objective, a new group of subjects performed the same task on a real patient and were studied using the same assessment methods. Scores between the two groups were then studied for statistical differences.

Lehmann [35] compared a Virtual Endoscopic Surgery Trainer (VEST) and a Conventional Video Trainer (CVT). The purpose of this study was to determine if skills based in a virtual reality setting transferred to a real world setting. Both trainers were designed to train and assess the users visuospatial, perceptual, and psychomotor skills. The physical models for the CVT were exactly recreated from the virtual computer models in the VEST.

Brehmer [34] discusses her validation of an ureterscopy bench model from Mediskills via comparison with real patient procedures. She provides the task-specific checklist and

global score used in the study where 14 participants were evaluated performing the procedure twice on patients (due to variability) and once on the bench model. She also briefly describes the validation studies performed on the ADEPT and MIST-VR systems.

Grober [28] studied the relative attributes and educational effectiveness of live animal models versus synthetic training models on the acquisition and maintenance of surgical skill using a microsurgery research platform. Three groups were studied: high-fidelity rat vas deferens [a vessel of the reproductive tract], low-fidelity silicone tubing, and didactic “paper and pencil” training. The subjects were evaluated based on patency of anastomosis, suture placement precision, and overall quality. They found that the “low-fidelity bench model conferred the same degree of benefit as training on a high-fidelity model”. Both models were superior to the didactic approach.

4.1.5 Surgical Simulators – As Part of a Full Training Curriculum

The surgical simulator is only one part of the surgeon’s training. The maximum learning comes when a surgical simulator is integrated as part of an entire training curriculum.

Chitwood [40] provides an outline of a surgical training curriculum for robotic surgical systems. The principles presented are transferable for a surgical training simulator.

Chitwood’s table is reprinted below (Table 2).

Table 2: Table 1 from [40], robotic surgical training curriculum.

Table 1. ROBOTIC SURGICAL TRAINING CURRICULUM LEVELS	
I. Didactic overview	<ul style="list-style-type: none">● Understand robotic vision and electronics● Understand robotic instrumentation● Understand robotic ergonomics● Understand robotic limitations
II. Inanimate laboratory	<ul style="list-style-type: none">● Master operative console● Master robotic operative cart● Master instrument and camera control
III. Animal laboratory	<ul style="list-style-type: none">● Console surgeon—master suturing, tissue cutting, suture tying● Patient-side assistant—master:<ul style="list-style-type: none">○ Instrument exchanges○ Camera cleaning○ Cauterization○ Clip application○ Retraction○ Trocar positioning
IV. Cadaver laboratory	<ul style="list-style-type: none">● Master trocar positioning● Apply I-III to human anatomy● Apply I-III to variable body habitus
V. Operative observation	<ul style="list-style-type: none">● Determine differences from I-IV● Observe interaction with adjunctive surgical technology

The guiding theme is to gradually build the student’s skill level with as much realism as possible: first with the instruments alone, with use in an inanimate lab (simulator), with use on live tissue (animal), with use on human anatomy (cadaver), and finally on a live human patient.

Weidenbach [41] focuses further on the visualization aspect of cardiac surgery. This paper describes a simulator and training curriculum specifically for echocardiography making the point that “echocardiographic simulators should use real ultrasound images to train the necessary perceptive skills that are needed to analyze the images that often differ

from the trainee's mental concept of heart images, especially when they are distorted by backscatter noise and artifacts.”

Here again, the emphasis is on training as close to reality as possible.

4.2 Surgical Training Simulators For Cardiac Surgery

This section focuses on existing surgical simulators specifically for cardiac surgical procedures. This section goes on to describe other aspects of heart function simulation: 1) the beating heart and 2) pulsatile flow systems.

4.2.1 Surgical Simulators - Cardiac Specific Trainers

The following discusses three examples of beating heart trainers. Stanbridge [38] described the Pulsatile Beating Heart Model (Figure 13) (part # 40503, no longer in production) produced by Limbs and Things, Ltd. (Bristol, U.K.) and its effectiveness in anastomoses training (the stitching of two vessels together such as in bypass surgery). The training model mimicked outer skin, pericardium, fat pads, ribs, intercostals tissues, vessels, chest cavity, and a beating heart. The heart was inflated at 60 beats per minute for the study.

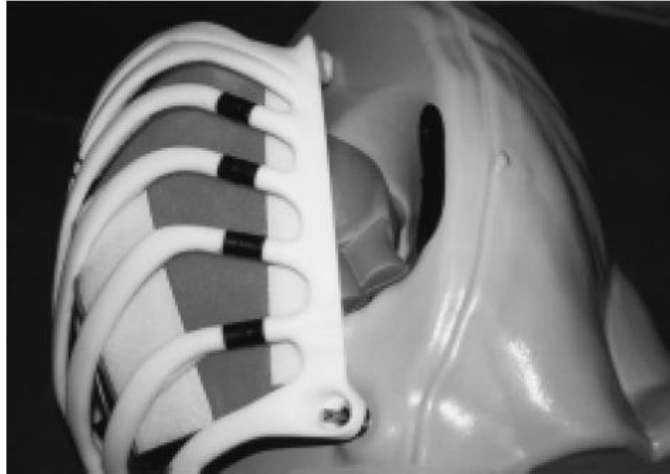


Figure 2. Heart within Thoracic Cage

Figure 13: Figure 2 from [38], an image of the Pulsatile Beating Heart Model. Model (part # 40503, no longer in production) by Limbs and Things, Ltd. (Bristol, U.K.) without the skin flaps.

The beating heart was intended for practice operating on vessels on the surface of the heart and did not contain any internal heart anatomy (such as valves or chordae tendinae).

Briefly, groups of participants with varying surgical experience were scored on their performance after differing amounts of practice with the simulator. The primary evaluation metrics were neatness, patency, and time. After practice on the simulator, the overall performance of the participants increased. Additionally, the training simulator proved to be effective.

While the focus of von Segesser's [42] paper was on training of a new surgical technique, it contained several images from the Heart Lab International in Stans, Switzerland (Figure 14). Their realistic chest phantoms contain preserved porcine thoracic organs. These provide a very realistic option for surgeon training.



Fig. 3. Realistic chest phantoms with preserved porcine thoracic organs (Heart Lab International, Stans, Switzerland) ready for hands-on less invasive aortic valve replacement (video equipment by Treier/Wolf, Beromünster, Switzerland).

Figure 14: Figure 3 from [42], an image of the Heart Lab International, Stans, Switzerland.

The chest phantoms with preserved porcine organs are the focus of the figure.

The Zurich heart-trainer that Reuthebuch [43] describes was mainly developed to train coronary artery bypass grafting (Figure 15).

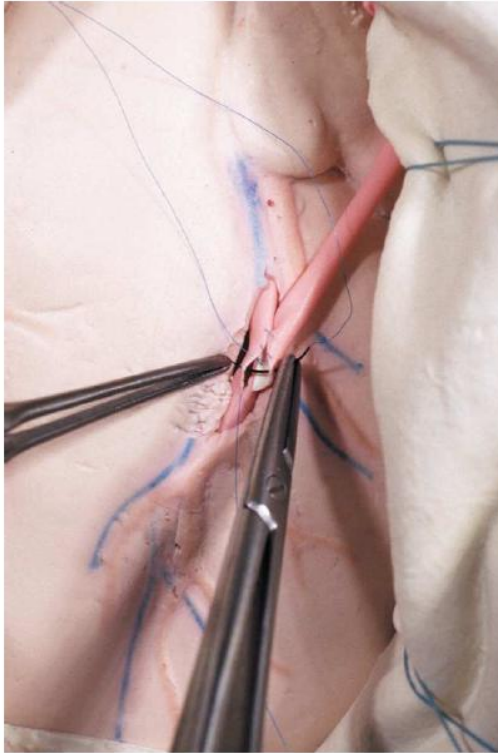


Fig. 8. Vessels are water-tight and can be rinsed with saline to control tightness of anastomoses.

Figure 15: Figure 8 from [43], an image of a practice anastomosis.

The caption reads “Fig. 8. Vessels are water-tight and can be rinsed with saline to control tightness of anastomoses.”

The trainer replicates a human chest cavity, embedded skeletal elements, inflatable lungs, the Great vessels, and a beating heart. The lungs and heart are inflated via an air pump.

The heart beat can duplicate a range of heart rates. The polyurethane vessels are available in different sizes, stiffness, and levels of disease progression.

As summarized, many of the existing cardiac surgeon training simulators consist of anatomically correct components. They focus on pulsatile motion for the exterior features of the heart and train for those related surgical procedures.

4.2.2 Beating Heart and Pulsatile Flow Systems

The next progressive step is to simulate the interior features of the heart including the valves and chordae tendinae. This section focuses on two methods: beating heart systems and pulsatile flow systems.

Beating heart systems refer to systems that reperfuse actual hearts (restart excised animal or cadaveric hearts) using a system of external pumps and/or stimulation (mechanical or electrical) of the heart muscle.

Pulsatile flow systems duplicate the heart's blood pressures and flow patterns but do not necessarily mimic the heart's anatomical proportions or appearance. The general purpose of these systems is to recreate physiological flows of the heart to accurately study and test mechanical, prosthetic, and other engineered valves. These systems could potentially be altered to accommodate surgeon training on a beating heart.

Vermette's [44] paper states requirements that pulsatile systems must achieve to accurately replicate the physical output of the heart. The table is included below (Table 3).

Table 3: Table 1 from [44], general requirements for the continuous and pulsatile flow circulation system.

TABLE 1. *General requirements for the continuous and pulsatile flow circulation system*

Functional
To circulate a continuous or pulsatile flow through small diameter conduits.
Technical
Transmural pressure up to 500 mm Hg
Flow rate up to 6,000 ml/min
Frequency of pulsation from 0 to 4 Hz
Adjustable pulsatile amplitude
Adjustable temperature from 20 to 37°C
Minimization of the flow volume system
Nonreactive materials construction
Minimization of the disturbances at the prosthesis anastomosis

Beating Heart Systems

Chinchoy's [45] paper describes the beating heart system at the University of Minnesota. The component details and setup schematics are provided in the paper's Method Section. The paper covers animal preparation, *in vivo* and *in situ* measurements taken, apparatus setup details, imaging performed inside the beating heart, and pressure measurements in different sections of the beating heart at varying phases in the cardiac cycle.

From the University Hospital of the West Indies in Jamaica, Craven and Ramphal describe "a system to simulate a beating human heart using intra-ventricular balloons, which are inserted inside a preserved *in vitro* porcine heart and made to pulsate using a pneumatic pump" [46]. Bovine coronary arteries were used for bypass operation training. One pump is used to simulate the beating heart and another is used to pump fluid through the coronary arteries. Craven [46] details the system design – both requirements and

outputs. While Ramphal [47] provides a nice schematic diagram of the simulation scenario in the Method's Section, the main purpose of the paper looks at the use of the system for surgeon training. The main procedure tested was an aortic valve replacement. This particular paper concludes that the simulator provides hi-fidelity tissue interaction for the training surgeon; however, more funds are needed to continue the study.

In summary, the biological beating heart systems use excised hearts. They provide highly accurate simulation of the heart's internal and external features; however they have obvious reusability/longevity limitations due to the actual tissue. Pulsatile flow systems provide a more mechanical alternative.

Pulsatile Flow Systems

Jensen [48] briefly describes the Georgia Institute of Technology's (Georgia Tech's) Left Heart Simulator. Earlier versions resembled beating heart systems. The version of the simulator described here focuses on recreating left ventricular flows. This simulator allows controlled displacement of the papillary muscle-chordae tendinae-mitral valve construct. Additionally, the simulator is capable of recreating left ventricular flows in normal and diseased hearts. The remainder of the paper presents the findings of papillary muscle force relating to varying positions and transmitral pressures.

The papers by Rambod [49] and Milo [50] describe the left heart pulsed flow simulator used in the Cardiovascular Fluid Dynamic Research Laboratory at the California Institute of Technology (Caltech). The component details along with a setup schematic are provided in each paper's Method Section. The major components are a positive

displacement pulsatile pump, a waveform generator, a left ventricular compartment, two pressurized chambers, and an open reservoir (Figure 16).

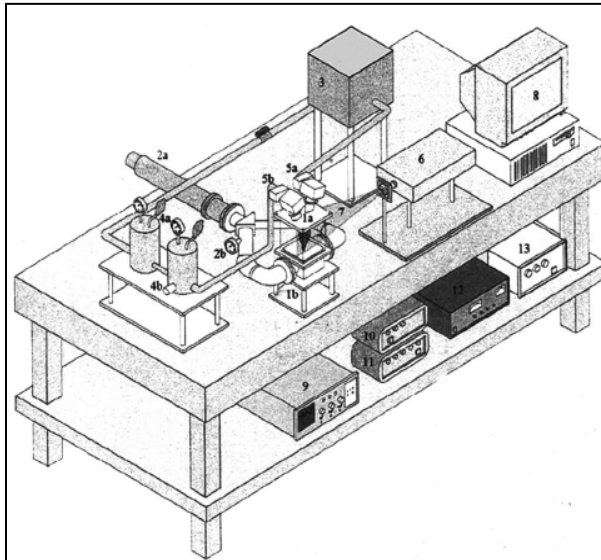


FIGURE 1. Schematics of Caltech's left heart pulsed flow simulator: (1a) left ventricular compartment, (1b) a stand to provide access from beneath, (2a) positive displacement pump, (2b) pressure monitoring device, (3) open-to-atmosphere venous reservoir, (4a) compliance and systemic resistance chambers, (4b) output for monitoring liquid's gas content, (5a) in-line ultrasonic flow probe (mitral), (5b) clamp-on ultrasonic flow probe (aortic), (6) YAG:Nd double pulse laser, (7) laser light sheet for illumination, (8) computer and data acquisition system, (9) scope, (10) wave form generator, (11) pump driver, (12) ultrasonic flowmeter, (13) electronic pressure sensor.

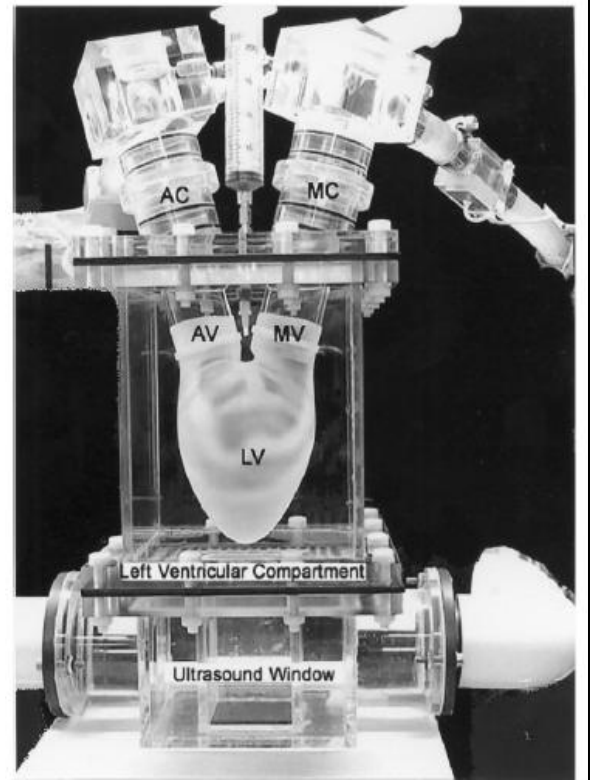


Fig. 3. Left heart pulsed flow simulator. LV, left ventricular sac; MV, mitral valve; MC, mitral channel; AV, aortic valve; AC, aortic channel.

Figure 16: The California Institute of Technology's left heart flow simulator.

Figure 1 from [49] and Figure 3 from [50]. Figure 1 shows a full schematic of the Caltech system. Figure 3 shows a close-up of the left heart flow simulator.

Rambod [49] focuses on the construction of the system, the mathematical equations governing the model, and the system's validation. Milo [50] focuses on testing performed to study heart valve implants. Kheradvar [51] focuses on prosthetic mitral valve testing with the Carpentier-Edwards Perimount valves.

Gao [52] describes and provides the schematic for a mock physiological flow loop. Briefly, it consists of a pneumatically driven pump, a collecting reservoir, several compliance chambers in series, an aortic testing channel, and a ventricular box divided into two compartments by a natural-rubber latex diaphragm. In this particular paper, a bovine pericardial bioprosthetic aortic heart valve was studied. The system incorporates two cameras to capture leaflet motion using the dual camera stereo photogrammetry technique. (By placing ink markers on the leaflet, transient geometry of the leaflet surface during the heart beat cycle can be captured. The three-dimensional deformed surface can be recreated and stress-strain analysis under dynamic conditions can be studied [52]).

Colacino [53] describes a hydraulic mock circulatory system for testing cardiac assist devices such as Left Ventricle Assist Devices (LVADs). Briefly, the system used in this paper contains four chambers: one pump, two air trapped reservoirs, and one open reservoir. The details of the components and the guiding mathematical models are well laid out in the Materials and Methods Section. The paper showed initial promise in the interaction of the physical output and the mathematical models. A more sophisticated pump controller is under development to make a more robust simulator.

ViVito Labs has developed many pulsatile flow pumps and systems along with the corresponding programming to produce waveforms mimicking physiological rates. Two examples are the Pulse Duplicator System and the Model Left Heart System (Figure 17). The primary function of these systems is to test artificial heart valves [54].

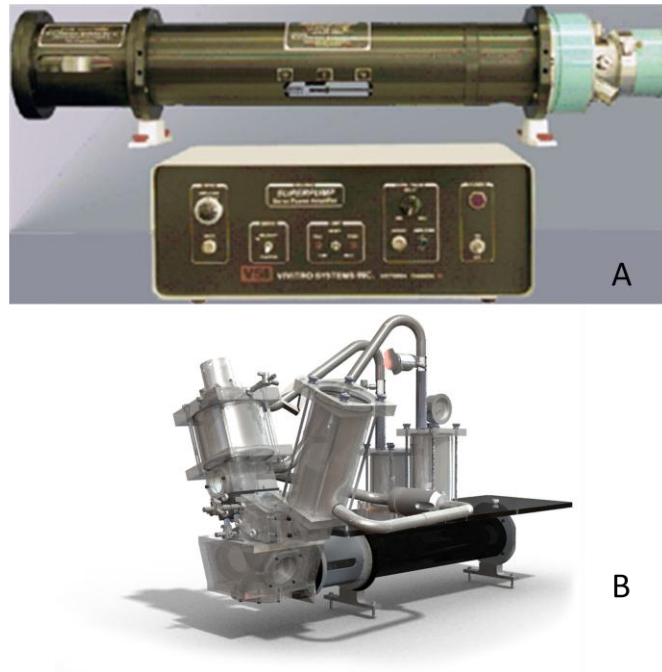


Figure 17: ViVibro's Pulse Duplicator (A) and Model Left Heart (B) systems [54].

Vermette [44] describes a design for a circulatory system that is capable of both pulsatile and non pulsatile flow. The system is composed of a feed tank, a pump, a heater, three metering valves, a regulating flow tank, a fixation rig located in a closed reservoir, and a pulsatile mechanism. The purchased and custom built component details along with the setup schematic are provided in the paper's Method Section. The remainder of the paper provides the output data used for validation of the system.

Vandenberghe [55] also describes a system that has continuous and pulsatile flow modes. The component details along with a setup schematic are provided in the paper's Method Section. Briefly, the setup consisted of a pneumatically driven heart simulator, a rotary blood pump, an afterload section, and silicon left atrium and ventricle. Much of the

experimentation correlates different pump setting combinations to heart rates. The paper also investigates energy consumption of the studied setup to optimize efficiency.

In summary, pulsatile flow systems offer reusability not easily achievable with the real tissue of the beating heart systems. They are capable of simulating a wider range of physiological conditions; however lack the external anatomical correctness seen with current cardiac simulators.

Other Systems

Lim [56] presents a simpler, non-pulsatile, steady flow system used for evaluating the performance of mechanical, caged-ball, and bioprosthetic heart valves. The paper starts with a brief description of the apparatus setup, schematic, imaging technique (Particle Image Velocimetry), and modeling equations (Reynolds Number) used. Velocity vector fields are presented from computer models as well as the visualized physical flows from the experiments (created by introducing air bubbles to the fluid flow).

Pantalos [57] describes a mock adult circulation loop system. However, this system does not use an actual heart. The component details along with a setup schematic are provided in the paper's Method Section. The system consists of an atrium, ventricle, and vascular components. All are made primarily from polyurethane. Mock circulation pressures, flows, and volumes were measured. The Results Section describes the outputs seen with the system and how it correlates to a real physiologic system. For example, "ringing" in the aortic waveform was filtered using MATLAB. Depending on the difference, the pressure-volume loops between the inflow and outflow can correlate to stiffer ventricles

or poor contractile function. This system can simulate various abnormal conditions of the functioning heart ranging from normal to a failing heart to a cardiac recovery.

Ferrari [58] investigated a method to combine numerical modeling with a hydraulic model of a circulatory system linked via an electrohydraulic interface. The component details along with a setup schematic are provided in the paper's Method Section. The paper describes the physical setup involving the gear pump, motor, tachometer, and servoamplifier used in the physical system. Additionally, the combining of software and hardware is described. In the experimental part of the paper, pressures as a result of varying ventricular volumes were studied to validate the system for those parameters.

In summary, these systems provide further examples of what can be simulated using a mechanical approach.

CHAPTER 5- SURGICAL SIMULATOR - THE MITRAL HEART VALVE

Chapter 4 discussed the growing need for surgical training simulators and provided evidence showing that validated simulators are effective training tools. It further illustrated the current status of cardiac-related simulators (good external heart features but no internal features), the drawbacks of beating heart systems (poor reusability/longevity), and pulsatile flow systems (good internal heart features but no external features).

This chapter will outline the development plan for a beating mitral valve surgical simulator by taking the relevant aspects of what is currently successful (Chapter 4) and apply that to a product development cycle – using the outline presented in Chapter 2. It will conclude by further utilizing information presented in Chapter 3 to outline how an existing device (the NeoChord DS1000) can aid in the development of the simulator.

5.1 Drawbacks of Current Cardiac Surgery Training Simulators

Section 4.2 provided a summarized view for aspects of cardiac surgery currently being simulated. However, existing training simulators have drawbacks relating to the simulation of beating heart valve surgery (and in particular the mitral valve). This is the case since the current standard of treatment for Mitral Valve Regurgitation (MR) is open-heart surgery while the heart is stopped and on by-pass.

Current beating heart simulators (cardiac surgical simulators) are primarily for surgeries on the heart's surface. They provide useful examples for simulating the external beating heart surface, but they do not accommodate internal structures, including valves.

Beating heart systems that reperfuse hearts have limited reusability/longevity due to the use of actual tissue.

Current pulsatile flow systems focus on the evaluation testing of valves. They provide useful examples for simulating valve motion with flowing liquid, but their chambers are sealed and not designed to be accessed by surgical tools. The flows produced are physiologically accurate, but the systems make little attempt at anatomical correctness when mimicking other components of the heart.

Therefore, there exists an unmet need for a surgical training simulator for heart valve surgery that incorporates the beating heart, anatomically correct heart anatomy (both internal and external) and leaflet motion, physiologically correct flow rates, and the ability to interface with surgical devices.

5.2 Development Outline: Surgical Training Simulator for the Mitral Heart Valve

Chapter 2 can be followed to create a development plan or outline for a surgical training simulator for the mitral valve. Following the flow charts presented earlier (Figure 7, Figure 9, Figure 12) an example plan is described below.

5.2.1 Concept Generation

The general concept has been provided by the unmet need: a surgical training simulator for heart valve surgery that incorporates the beating heart, anatomically correct internal and external heart anatomy and leaflet motion, physiologically correct flow rates, and the ability to interface with surgical devices with the purpose of training surgeons for beating-heart valve repair procedures.

The complexities of the very initial concepts for a simulator specifically for the DS1000 ranged broadly from simple silicon models of the left ventricle to fully immersive simulated operating rooms. Resources, including funding, for the project were reallocated away before the scope of the project could be narrowed.

Therefore, in the sections that follow, the author presents a general simulator development plan with provided examples based the following simulator concept.

Utilizing the knowledge from successful existing simulators (1) section 4.2.1 addressing current simulators for cardiac surgery procedures on the surface of the heart and 2) section 4.2.2 addressing methods to simulate the beating internal features of the heart) the physical form of the mitral valve simulator starts to take shape. Pumps, reservoirs, wave form generators, controllers, synthetic tissue structures, and anatomically correct features are all likely component parts. Figure 18 is the author's provided example schematic incorporating these physical features together. Further details are provided in section 5.2.5.

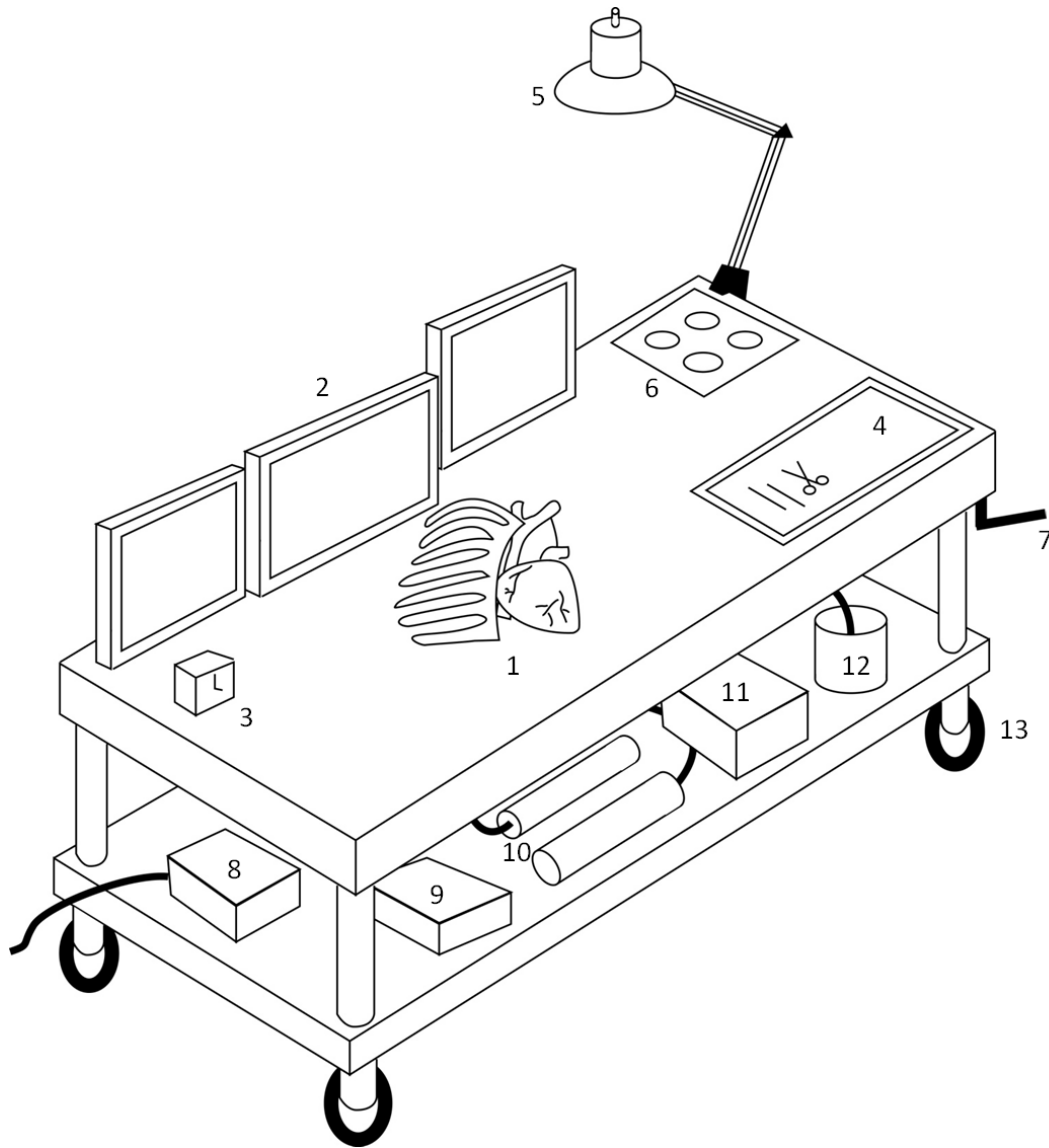


Figure 18: Schematic Layout for the example Mitral Valve Simulator.

Components include: 1) simulated beating heart, chest cavity, rib cage, skin and fat layers, 2) monitors and displays, 3) timer/clock, 4) tray for surgical instruments, 5) spot lighting, 6) container for exchangeable valves, 7) table height adjustment, 8) power adapter, 9) electronics controller / waveform generator, 10) pumps, 11) reservoir, 12) pressure tank, and 13) wheels.

5.2.2 Simulator Requirements Specifications

Several components feed into the simulator's system requirements specifications (Figure 9). In the following section, the author provides example system requirements for the mitral valve simulator concept provided (Figure 18).

The unmet need and the general concept provide several functional/performance requirements. The simulator must be anatomically correct for both internal and external features. The physiological flow rate must be accurate. This includes the pulsations and liquid volumes for heart rates that may be experienced during surgery (normal and abnormal – slower and faster (including erratic)). The simulator should be able to accommodate different severities of diseased valves that will be experienced during operations on a diverse patient population.

The general surgical procedure provides several form/size requirements. Section 1.1.2, along with Falk [20], provides a basic description of the mitral valve repair surgical procedure (general steps include access via a thoracotomy in the intercostal space, opening the heart atrium or ventricle, attain a visual of the valve, place and tension the sutures, secure the knots, and the final closing of the patient). Kypson [21] proposes aspects of the ideal cardiac valve operation including tiny incisions, antegrade perfusion, tactile feedback, eye-brain visualization, secure valve attachment, and no instrument conflicts with the minimally invasive access. The simulator can be tailored for a specific instrument's surgical approach or designed robustly, accommodating a variety of different surgical devices/approaches. Regardless, the simulator must contain components addressing each of the aforementioned attributes. Other size considerations depend on the

environment of intended use (e.g. a simplified, portable bench top model versus a fixed, immovable, robust system).

The simulator's teaching/learning objective(s) should be considered here as well. Each aspect of the surgical procedure that is intended to be taught using the simulator must have that feature designed in. This includes disease diagnosis/progression assessment, surgical access, device usage, and closure.

Exchangeability and expandability of components should be considered for the simulator at this point. It will likely be beneficial to have exchangeable or replaceable valve leaflets available as the installed ones wear from use. One can also consider different types of leaflet replacements. For example, valves at different stages of disease progression (varying annulus size, regurgitation severity, and leaflet thickness) could be considered. Finally, consider a simulator design to accommodate further expansion for other anatomy (such as the great vessels, or surrounding organs and bones). Life cycle costs (maintenance, repair, upgrades, etc.) over the lifetime of the simulator should be assessed at this point.

FDA regulation 21 CFR 820.30, as part of the Quality System's design control, requires, in part, documentation of design inputs (system requirements), the translation of the inputs into design requirements (design specifications), and the confirmation that the requirements have been met (verification and validation testing). However, the regulation does not require a specific template or format. The exact form is left to the individual to develop.

An example System Requirements Specification is provided (Table 4) for the example concept MV Simulator (Figure 18). The table template is based on that developed for the DS1000. To comply with the categories put forth by the regulation, the template contains a section to document the system requirement, to explain the rationale or intent, to document the translated design requirement(s), and a section to document verification of the requirement. To assist with requirement development/documentation, the template also provides broad categories of that should be considered at a minimum: Functional, Performance, User Interface, Environmental, Safety, and Regulatory requirements.

The detailed content is provided by the author as examples based on the concept MV Simulator (Figure 18). The interested reader can use the examples as a guide to create a specific System Requirements document for a specific simulator. The provided examples are meant to be non-exhaustive, thought-provoking, and illustrate the wide range of topics to consider. The column for Design Requirements is left as to-be-determined (TBD) in this example. The interested reader, for one's specific design, will populate this section with design specification. These specifications guide development of (but not limited to) design prints, requirements documentation, manufacturing instructions/precautions, and the Instructions for Use. Furthermore, the columns for verification and validation are currently marked as the likely testing format wherein the example requirement would be best tested (e.g. in a mechanical test (MDVT), an electrical test (EDVT), a Simulated Use Test (SUT), etc.). At this stage, it provides an overview of what testing will need to be planned for as the project progresses. Further in the project, this section can be updated to document the specific test report sections where the specific requirement was tested.

Table 4: System Requirement Specifications Example for a Mitral Valve Simulator

SRS#	System Requirement Specification (SRS) Functional Requirements (FR): Physical features / Aesthetics	Rationale	Design Requirement	Verification and Validation							
				MDVT	EDVT	Ship/Pack/ Shelf Life	Bio- compatibility	Labeling	Simulated Use		
101	Must have capabilities for physician training and product design testing.	To train physicians or evaluate devices.	TBD								x
102	Must have capabilities for surgical and vascular approaches to heart valves.	To train surgeons or interventionalists. To evaluate surgical or interventional devices.	TBD								x
103	Must be portable and have minimal components and assembly.	For ease of transportation and assembly.	TBD	x							x
104	Must be capable of shipment via standard modes (e.g. ground, air, rail, water).	For ease of transportation.	TBD					x			x
105	Must comprise of a beating heart exterior and moving valves interior with realistic materials and textures.	For accurate simulation of beating-heart valve procedures. The combination addresses the unmet needs of current simulators on the market.	TBD								x
106	Must contain simulated features: ribs, intercostal space, great vessels, heart chambers, moving valves, chordae tendinae, papillary muscles, flowing media, beating heart exterior.	For accurate simulation of beating-heart valve procedures.	TBD								x
107	Must have anatomically correct dimensions for all simulated features.	For accurate simulation of beating-heart valve procedures.	TBD	x							
108	Simulated features must be exchangeable/replaceable: valves, pumps, chambers, hardware.	For variety of simulations and maintenance of simulator.	TBD	x							x
109	Must contain standard Operating Room monitor displays (display screen and information/content). E.g. TEE, ultrasound, patient vital signs.	For accurate simulation of beating-heart valve procedures.	TBD								x
110	Must contain imaging modalities including TEE, MRI, CT, fluoroscopy.	For accurate simulation of beating-heart valve procedures.	TBD								x
111	Must provide spot lighting equivalent to Operating Room conditions.	For accurate simulation of beating-heart valve procedures.	TBD								x

Performance Requirements (PR): During and After Use										
201	Must have physiologic flow rates, volumes, pressures.	For accurate simulation of beating-heart valve procedures.	TBD	x						
202	Must simulate heart beat conditions possible during surgery: normal, slowed, elevated, erratic, fibrillating, stopped.	For accurate simulation of beating-heart valve procedures.	TBD							x
203	Cutting/suturing tissues must be capable of multiple uses and be exchangeable/replaceable: intercostal space, heart muscle (apex), valve leaflets.	For variety of simulations and maintenance of simulator.	TBD	x						x
204	Instrumentation guidance must be accomplished using standard imaging modalities (TEE, MRI, CT, Fluoroscopy, etc.)	For accurate simulation of beating-heart valve procedures.	TBD							x
205	Simulated imaging guidance must account for real-life distortions, backscatter noise, and artifacts.	For accurate simulation of beating-heart valve procedures.	TBD					x		x
206	Simulator must provide accurate tactile feedback to the user.	For accurate simulation of beating-heart valve procedures.	TBD	x						
207	Simulator must provide accurate imaging feedback to the user.	For accurate simulation of beating-heart valve procedures.	TBD					x		
208	Simulator must measure and display desired metrics: session time, economy of movement, smoothness of movement, accuracy.	For evaluation of training or evaluation session.	TBD							x
209	Must simulate varieties of heart valve leaflet conditions: healthy, calcified, myxoid, thinning, frail, different stages of disease progression.	For a variety of simulations. For accurate simulation of beating-heart valve procedures.	TBD							x
210	Must simulate varieties of heart valve conditions: normal, stenotic, prolapsing.	For a variety of simulations. For accurate simulation of beating-heart valve procedures.	TBD	x						x
211	Must simulate varieties of annulus shapes and sizes.	For a variety of simulations. For accurate simulation of beating-heart valve procedures.	TBD							x
212	Must be capable of 4 hours continuous use minimum.	To allow adequate time for training/evaluation sessions.	TBD	x						x

User Interface Requirements (UR): Operator and Simulator									
301	Simulator must not interfere with instrumentation in any manner other than that experienced by anatomy.	For accurate simulation of beating-heart valve procedures.	TBD						x
302	Must limit visualization of heart-instrument interaction to mimic that of the surgical procedure. Must additionally allow optional full visualization.	For accurate simulation of beating-heart valve procedures. Full visualization allows for additional learning or evaluating outcome of valve procedure.	TBD						x
303	Learning on simulator must correlate to learning in the actual surgical procedure.	For accurate simulation of beating-heart valve procedures.	TBD						x
304	Must have Internal Validity - repeated use improves performance regardless of user's experience level.		TBD						x
305	Must have External Validity - distinguish between user's experience level.	For effective learning from the simulator.	TBD						x
306	Must have Construct Validity - simulator accurately represents the actual surgery.	For effective learning from the simulator.	TBD						x
307	Height must be adjustable corresponding to an Operating Room table.	For accurate simulation of beating-heart valve procedures.	TBD				x		
Environmental Requirements (ER):									
401	Must be adaptable to United States and European electrical power outlet supply.	For use in diverse locations.	TBD					x	
402	Must not interfere with, or be interfered by, common electrical equipment.	For use in diverse locations.	TBD					x	
Safety / Regulatory Compliance Requirements (SR):									
501	Must contain labeling to warn of shock/danger/other hazards relating to use.	For user safety.	TBD						x
502	Must conform to general electrical safety standards.	For user safety.	TBD					x	
503	Must conform to general medical device safety standards.	For user safety.	TBD					x	
504	Must be comprised of non-toxic materials.	For user safety.	TBD						x
505	Must comply with applicable medical electrical regulatory and external standard requirements.	Compliance with applicable regulations and standards is required for sale and distribution in intended markets.	TBD						x

5.2.3 Simulator Requirements Specifications - Imaging

Another aspect to consider is imaging modalities/techniques. Should the simulator be designed to include different imaging techniques for a variety of surgical procedures (such as echocardiography, fluoroscopy, or x-ray)? If so, the simulator must accurately simulate the images seen in the actual procedure. This adds another level of complexity to the simulator design, but learning how to achieve the proper visualization for the surgical procedure is equally as important as learning the proper device manipulations.

Weidenbach's simulator is specifically for echocardiography training; however, several principles can be applied for imaging training for any surgical procedure. "While the medical knowledge in cardiology is quite effectively provided by textbooks, journals and lectures, the practical skills can only be achieved through hands-on training" [41]. The user must gain experience with the standard views, positioning the imaging instrument to achieve those views, correlating instrument position to the cross-sectional image produced, and identifying landmarks in each view. Additionally, the simulator must account for image fuzziness that occurs in reality due to distortions, backscatter noise, and artifacts. Furthermore, the simulator could provide real-time instruction to the user for achieving the optimal image.

Huang [24] describes imaging artifacts caused by various instrument shapes and materials (specifically using ultrasound). This background is useful in two major ways. First, with the aid of a training simulator, the user can learn what the instrumentation will appear as under imaging and what distortions and artifacts to expect. Further skill refinement will lead to techniques to minimize distortions by properly positioning the instrument relative to the imaging probe. Second, this knowledge can be used in the

design of the instrumentation itself. Materials and geometry can be selected up front with imaging compatibility in mind.

5.2.4 Regulatory Standards

The medical device simulation industry is not as heavily regulated as the aviation simulation industry. However, this will change as the usage of surgical simulators becomes more critical in the training of physicians (section 4.1.1). As the regulatory agencies establish themselves, so too must simulator developers ensure diligence to comply.

5.2.5 Design

Taking the aforementioned inputs under consideration, the design must meet all the desired requirements.

As a starting point for a mitral valve surgical simulator, the relevant aspects of the existing beating heart and pulsatile flow simulators should be combined to meet both desired aspects of the new simulator.

Beating heart systems that reperfuse actual hearts are highly accurate but have the reusability/longevity limitations of the actual tissue. Actual leaflets or existing cardiac tissue alternatives (such as bovine pericardium) should be considered for the simulator leaflets. The tactile feedback from interacting with this tissue is a critical part of valve repair procedures and should be highly accurate.

Current cardiac simulators contain examples of accurate external elements. The mitral valve simulator should consider containing skin, ribs, intercostal space, and accurate exterior heart anatomy.

Existing pulsatile flow systems contain examples of how to incorporate flapping valves into a mitral valve simulator. General components include pumps, reservoirs, and a waveform generator.

Finally, imaging must be incorporated. Beating heart operations will rely on imaging techniques since incision sizes (and direct visualization) will be minimized. Current guidance modalities include TEE, CT, MRI, and fluoroscopy.

As introduced in section 5.2.1, Figure 19 (Figure 18 repeated below) is the author's provided example schematic incorporating these physical features together.

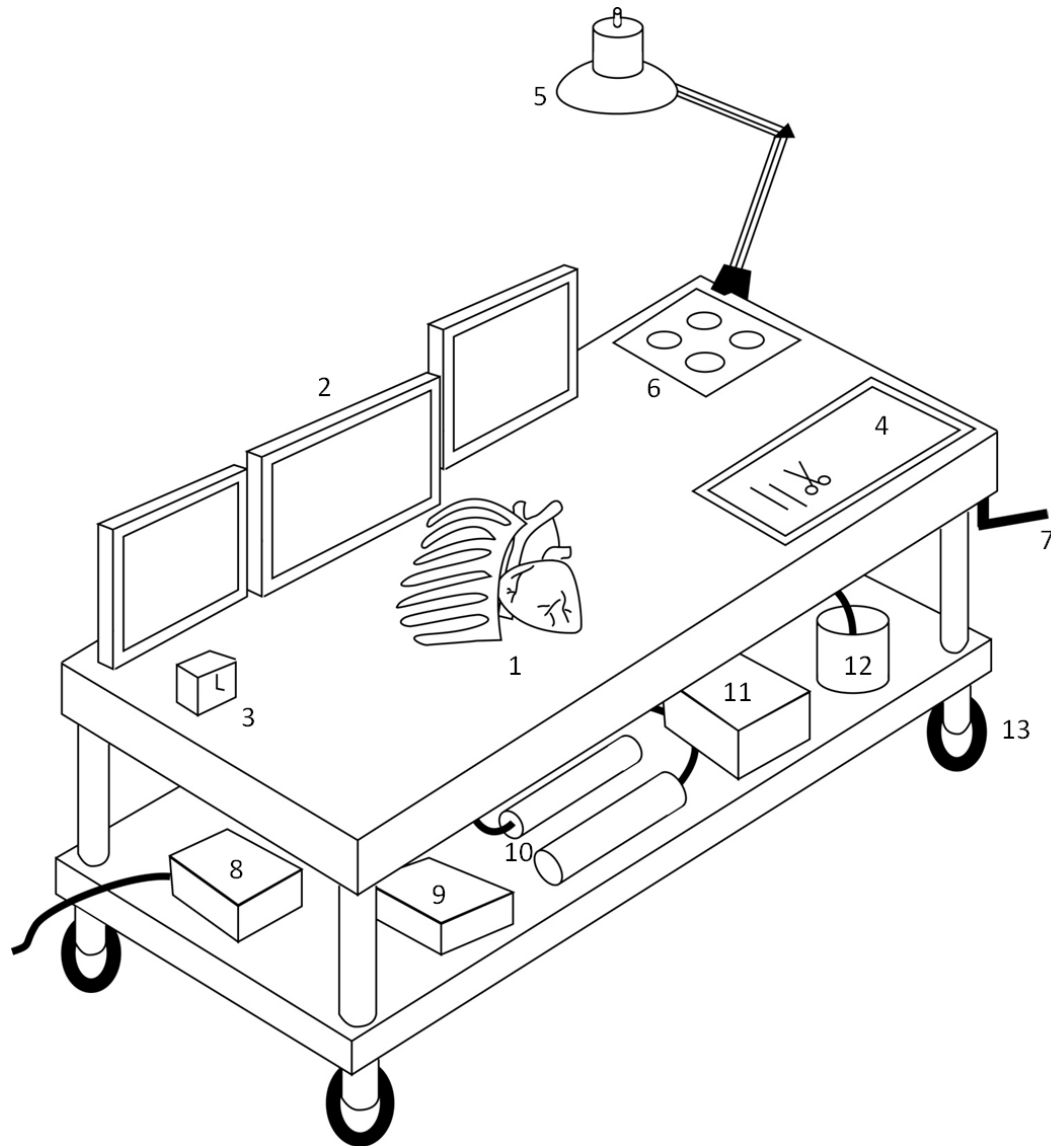


Figure 19: Schematic Layout for the example Mitral Valve Simulator (repeated).

Components include: 1) simulated beating heart, chest cavity, rib cage, skin and fat layers, 2) monitors and displays, 3) timer/clock, 4) tray for surgical instruments, 5) spot lighting, 6) container for exchangeable valves, 7) table height adjustment, 8) power adapter, 9) electronics controller / waveform generator, 10) pumps, 11) reservoir, 12) pressure tank, and 13) wheels.

In the provided example the simulator platform represents an operating room environment. The table's height is adjustable. Centered on the table is the simulated heart

encompassing accurate external surface appearances (vessels and muscle texture), anatomically and physiologically correct internal heart features (valves and flow rates), and the ability to interact with surgical instruments. An alternative option is to have the heart composed of a transparent material such that the operator, while still in the learning stages, can see the manipulations being performed on internal tissue structures. This will aid in acquiring proper muscle memory for performing the actual procedure in which direct vision will likely not be possible.

Surrounding the heart is a mock chest cavity, rib cage, skin and fat layers, and other body elements useful for training surgical access techniques to the heart.

In the line of site of the user are several displays and monitors. Information displayed mimic live surgery data such as patient vital signs (heart rate, blood pressure, oxygen level) and image guidance (echo, ultrasound, fluoroscopy, MRI). Additionally, real-time feedback of the user's performance on the simulator can be displayed (training session time, evaluation metrics, technique improvement feedback).

Within close reach of the simulator's operator, as with a surgeon in the operating room, is a tray to hold surgical instrumentation (scalpels, sutures, scissors, devices) and a spot light for focused illumination. Furthermore, a container holds several replacement valves. Valves will deteriorate over time with use. Furthermore, several types/shapes of valves can be provided representing different stages of disease progression.

To keep the simulator relatively compact, the components required to facilitate the beating mechanics and flow rates will be secured under the primary tabletop. Pumps, controllers, waveform generators, tanks, and reservoirs can be secured underneath the

heart simulator and connected via necessary hoses, tubes, and cables. These examples were provided by the cited literature on pulsatile flow systems. Valve motion and heart beating mechanics were driven by pulsing liquid. Mechanical motors and actuators are an alternative to simulate valve motion. Inflatable sacs in the simulator's heart walls (pneumatically powered) are another alternative to simulating beating motions. The choices for how to mimic these motions results in fundamentally different designs and component requirements. The positives and negatives of each option should be carefully assessed in the early design stage. The complexity, development timeline, simulation accuracy, robustness (lifespan), and cost need to be compared with the allocated resources for the project to ensure the optimal design within the budget.

To keep the simulator relatively easy to move and store, the table can be situated on lockable wheels. Furthermore, a power supply that is adaptable to American and International power supplies will allow compatibility in an international market.

Several cycles of prototyping and proof-of-concepts will likely be required to turn this schematic of a concept into an actual simulator.

5.2.6 Risk Analysis

As the design phase progresses, risk assessments must be performed since these also guide the final design.

(Reference the List of Abbreviations, p. viii.) The FMEA or FMECA can be performed on the simulator from the standpoint of the simulator as a tool (a physical device). The CHA can be performed on the simulator from the standpoint of the simulated procedure

(the user interacting with the simulator). Consideration should be given to the following areas at a minimum:

- Risk of the simulator failing/breaking.
- Risk of the simulator harming the user.
- Risk of the user misusing and damaging the simulator.
- Risk of the simulator incorrectly simulating reality.

An example MV Simulator Hazards Assessment (Table 5) and FMEA (Table 6) follow for the concept MV Simulator (Figure 19). These will need revisiting as the design of the simulator progresses and takes a more concrete form.

ISO 14971 provides guidance for applying risk management to medical devices. It gives further guidance for qualitatively analyzing risk. The table template used in the examples is based on that developed for the DS1000 which, in turn, was created to comply with ISO 14971.

The Severity (S) of the risk was quantified using the following definitions:

<i>Severity Level Definitions (example)</i>		
<i>S Level</i>	<i>Description</i>	<i>Definition</i>
5	Catastrophic	Potential of death that cannot be readily mitigated by physician intervention.
4	Critical	Potential of death or serious injury requiring physician intervention.
3	Moderate	Potential of injury requiring physician intervention.
2	Slight	Little or no potential of injury. May result in physician intervention to replace product only.
1	Insignificant	Does not result in injury or product damage. May cause minor nuisance.

The Probability of occurrence (P) of the risk was quantified using the following definitions:

Occurrence Level Definitions (example)			
P Level	Description	Estimated Occurrence Rate	
		Fractional	Percent
5	Frequent	> 1/2	> 50%
4	Probable	1/10 to 1/2	10% to 50%
3	Occasional	1/100 to 1/10	1% to 10%
2	Remote	1/100 to 1/1,000	0.1% to 1%
1	Improbable	< 1/1,000	< 0.1%

The Risk Score is the summation of the Severity (S) and the Probability (P). It was categorized as follows:

Probability (P)	Severity (S)				
	5 <i>Catastrophic</i>	4 <i>Critical</i>	3 <i>Moderate</i>	2 <i>Slight</i>	1 <i>Insignificant</i>
5 <i>Frequent</i>	10	9	8	7	6
4 <i>Probable</i>	9	8	7	6	5
3 <i>Occasional</i>	8	7	6	5	4
2 <i>Remote</i>	7	6	5	4	3
1 <i>Improbable</i>	6	5	4	3	2

The final Recommendation was categorized as follows:

<i>Risk Index</i>	<i>Description</i>	<i>Definition</i>
8 - 10	Intolerable risk	The risk must be reduced to allow use of the product or a determination on the acceptability of residual risks may be made. Risks may be deemed acceptable if assessment determines benefits outweigh risks.
5 - 7	Moderate Risk: Acceptable	Risks are considered acceptable, and mitigation actions have been taken to reduce risks to the lowest level practicable, bearing in mind the benefits of accepting the risk and the cost of further reduction.
2 - 4	Broadly acceptable risk	The risk is negligible compared to the risk of other hazards which are accepted. For these hazards, risk reduction beyond product labeling need not be actively pursued

To comply with the categories put forth by the ISO standard, the template contains a section to identify the risk (hazard or failure), to evaluate the risk (the cause, the effect, the severity, the probability, and the total risk score), to identify where the risk is (or will be) controlled/mitigated, and a section to evaluate the residual of the risk post-mitigation.

The detailed content in the tables is provided by the author as examples based on the concept MV Simulator (Figure 19). The interested reader can use the example as a guide to create specific Risk Assessment documentation for a specific simulator. The provided examples are meant to be non-exhaustive, thought-provoking, and illustrate the wide range of topics to consider. The qualitative scoring of Severity and Probability were based on the author's best judgment of the example concept MV Simulator. The interested reader, for one's specific design, will populate this section with risks and scoring based initially on best judgments and later on documented occurrence rates from testing and usage.

The risk assessments aid in identifying aspects of the design that may need additional refinement or redesign. It is key that the risk assessment be an integral and ongoing process that is continually updated during the design stages.

Table 5: Hazards Assessment Example for a Mitral Valve Simulator

RISK IDENTIFICATION			RISK EVALUATION				RISK CONTROL				RESIDUAL RISK EVALUATION			
RM ID	Simulation Characteristic	List Hazard (hazardous situation exist?)	List Cause of Hazard	List Hazard Effect	S	P	Risk Score	Risk Control Recommended Actions	S	P	Risk Score	Recommendation		
1	Simulator Assembly / Setup	Simulator assembled incorrectly.	Directions not followed. Inadequate directions. Excessive number of parts.	Simulator fails to function / functions incorrectly. Harm to user. Inaccurate simulation.	3	2	5	Instructions for Use	3	1	4	Broadly Acceptable		
2		Damaged components.	Inadequate shipping container. Components not robust.	Simulator fails to function / functions incorrectly. Harm to user. Inaccurate simulation.	3	2	5	MDVT	3	1	4	Broadly Acceptable		
3	Beating Heart Simulation	Inaccurate simulation. Fluid leakage, pressurized fluid escape.	Beating heart system not validated. Excessive penetration into simulator with device/instrumentation.	Inaccurate simulation. Inaccurate user learning / evaluation. Leakage, harm to user, increased electrical hazard.	2	1	3	SUT	2	1	3	Broadly Acceptable		
4					3	2	5	EDVT, Instructions for Use	3	1	4	Broadly Acceptable		
5	Flapping Valve Simulation	Inaccurate simulation.	Flapping valve system not validated.	Inaccurate simulation. Inaccurate user learning / evaluation.	2	1	3	SUT	2	1	3	Broadly Acceptable		
6		Leaflet damage (rip, tear, dislodgement).	Excessive force applied to the leaflets by device / instrumentation.	Damage to simulator. Inaccurate simulation.	1	2	3	MDVT, SUT	1	1	2	Broadly Acceptable		
7	Imaging Simulation	Inaccurate simulation.	Imaging system not validated.	Inaccurate user learning / evaluation.	2	1	3	SUT	2	1	3	Broadly Acceptable		
8		No imaging guidance.	External imaging system not compatible with simulator.	Imaging system cannot be used. No imaging simulation / training possible.	1	1	2	Instructions for Use	1	1	2	Broadly Acceptable		
9	User Evaluation	Inaccurate simulation.	Failure of Metrics Measurement System. System not validated.	Inaccurate simulation. Inaccurate user learning / evaluation.	2	2	4	SUT	2	1	3	Broadly Acceptable		
10		Inaccurate user evaluation / feedback. Excessive simulator degradation / component replacements.	Failure of Metrics Measurement System. System not validated.	Incorrect or inaccurate user learning.	2	2	4	SUT	2	1	3	Broadly Acceptable		
11	Maintenance / Cleaning		Improper cleaning and maintenance.	Early and unexpected failure of the simulator. Harm to user.	3	1	4	MDVT, Instructions for Use	3	1	4	Broadly Acceptable		

Table 6: FMEA Example for a Mitral Valve Simulator

RISK IDENTIFICATION			RISK EVALUATION			RISK CONTROL			RESIDUAL RISK EVALUATION				
RM ID	Simulator Characteristic	FMEA: List Failure Mode	FMEA: List Cause	FMEA: List Failure Effect	S	P	Risk Score	Risk Control Recommended Actions	S	P	Risk Score	Additional Hazards	Recommendation
1	Assembly	Unexpected fluid leakage.	Incorrect assembly. Worn components. Worn seals.	User/surrounding area gets wet. Increased potential electrical hazard.	2	2	4	Instructions For Use	2	1	3	N/A	Broadly Acceptable
2	Assembly	Unexpected fluid leakage. Failure to function.	Incompatible exchangeable components used.	Simulator damage. Less effective or ineffective simulation/training.	1	2	3	Instructions For Use	1	1	2	N/A	Broadly Acceptable
3	Heart	Heart beats inaccurately. Heart fails to beat.	Pump failure. Waveform Generator failure.	Less effective or ineffective simulation/training.	2	1	3	MDVT, EDVT	2	1	3	N/A	Broadly Acceptable
4	Leaflets	Leaflets flap inaccurately. Leaflets fail to flap.	Pump failure. Waveform Generator failure.	Less effective or ineffective simulation/training.	1	1	2	MDVT, EDVT	1	1	2	N/A	Broadly Acceptable
5	Pump / Waveform Generator	Electrical malfunction.	Interferes with or interfered by an external electrical source.	Improper simulator function. Harm to user.	3	1	4	EDVT	3	1	4	N/A	Broadly Acceptable
6	Pump / Waveform Generator	Erratic pumping.	Pump/waveform generator malfunction.	Damage to simulator. Harm to user.	3	1	4	EDVT	3	1	4	N/A	Broadly Acceptable
7	Pumping Fluid	Simulator degradation.	Incompatible fluid used.	Simulator damage, leakage, component damage, harm to user, electrical hazard.	3	2	5	Instructions For Use	3	1	4	N/A	Broadly Acceptable
8	Imaging	No imaging guidance for instruments.	Incompatible imaging devices. Imaging failure.	Less effective or ineffective simulation/training.	2	2	4	Instructions For Use	2	1	3	N/A	Broadly Acceptable
9	Metric Measuring System	Inaccurate user evaluation/feedback.	Metric measuring system failure.	Inaccurate or ineffective learning.	1	1	2	EDVT	1	1	2	N/A	Broadly Acceptable
10	Maintenance	Clogged pump.	Debris (from worn leaflets, device, external contamination).	Pump failure.	2	2	4	Instructions For Use	2	1	3	N/A	Broadly Acceptable
11	Maintenance	Simulator degradation.	Improper cleaning and maintenance.	Simulator damage, leakage, component damage, harm to user, electrical hazard.	3	2	5	Instructions For Use	3	1	4	N/A	Broadly Acceptable

5.2.7 Design Analysis Testing

Design Analysis Testing can be performed as needed to ensure the simulator design meets the desired physical, anatomical, physiological, and educational attributes.

Refinements and retesting can be repeated as needed. Based on the example concept MV Simulator (Figure 19), examples of testing include:

Mechanical –

Measure physiologic dimensions of components, physiologic flow rates, physiologic pressures, and measure size and weight requirements relating to shipping.

Electrical –

Ensure electrical safety, electrical/radio compatibility, conformance with U.S. and international power supplies, and continuous operation duration.

Simulated Use –

Survey and incorporate surgeon feedback regarding realist feel. Test ability to measure desired evaluation metrics against a known standard (e.g. economy of motion, session time, and hand motion analysis).

5.2.8 Verification and Validation Testing

Here, the author provides general verification and validation testing examples based on background presented in section 4.1 for the example concept MV Simulator (Figure 19). The example System Requirements and Risk Assessment tables provide a preliminary idea of what types of testing will be needed.

Verification protocols are straight-forward to develop regarding physical attributes such as dimensions, flow rates, and failure limits listed above. For these types of tests, in general, the DAT will have proven the simulator meets the requirements, allowing the DVT to proceed with high confidence that it will pass.

If a simulator does not match reality, measured improvement only shows mastery in use of the simulator itself, nothing more. Sections 4.1.3 and 4.1.4 provide general guidelines and specific examples of existing methods used to validate surgical training simulators. The information provided in those two sections can be adapted to the example concept mitral valve simulator.

First, measurement metrics must be established. Metrics can be objectively or subjectively measured. They should relate to the actual surgical procedure. Improvement of these metrics on the simulator should correlate to improvement in surgery. Possibilities include overall neatness, procedure time, patency, hand motion analysis, economy and smoothness of movement, number of errors, accuracy, precision, navigation time to target, decision making, and overall realism as assessed by experienced physicians.

Once metrics are established, several groups of users will need to be assessed using the simulator and in the actual procedure. Groups should be distinguished by experience (novice, expert, non-surgeon, etc.).

Though validation test protocols will vary and be tailored to the specific simulator, the following general methods apply.

Internal validity – to show the simulator works, repeatedly evaluate users against the metrics. Users should improve regardless of experience level.

External validity – group users by experience level (novice, expert, non-surgeon, etc.). Analysis of the metrics should show a distinction between the groups.

Construct validity – to confirm that the simulator accurately represents the actual surgery, surveying of experienced surgeons will be needed. This can be performed for the overall simulator as well as the individual components. Additionally, compare the measured metrics of the same surgeon on the simulator and on the actual procedure. Correcting for individual patient anatomy and disease progression, metrics should be similar between the simulator and the surgery.

Finally, the same data set (comparing performance of users of differing skill on the simulator and in the actual procedure) should have a predictive quality. As skills improve with use on the simulator, a correlation to improved surgical performance should be evident.

5.3 Development Outline: Simulator Development Utilizing a Validated Device

This section further adapts the concepts presented in Chapter 3 to the simulator development plan outlined in the previous sections of this chapter.

The original intent (scope) of this thesis was to develop a surgical training simulator for the DS1000 in parallel to the device's development. The research presented in Chapter 4 is the background knowledge needed to aid simulator concept generation.

During the parallel development project, the company's priorities shifted. Resources, including funding, were reallocated away from the simulator and fully committed to the development of the device. With a validated DS1000 device, Figure 20 (Figure 12 repeated below) can be used to illustrate how that background knowledge can be used in the simulator development.

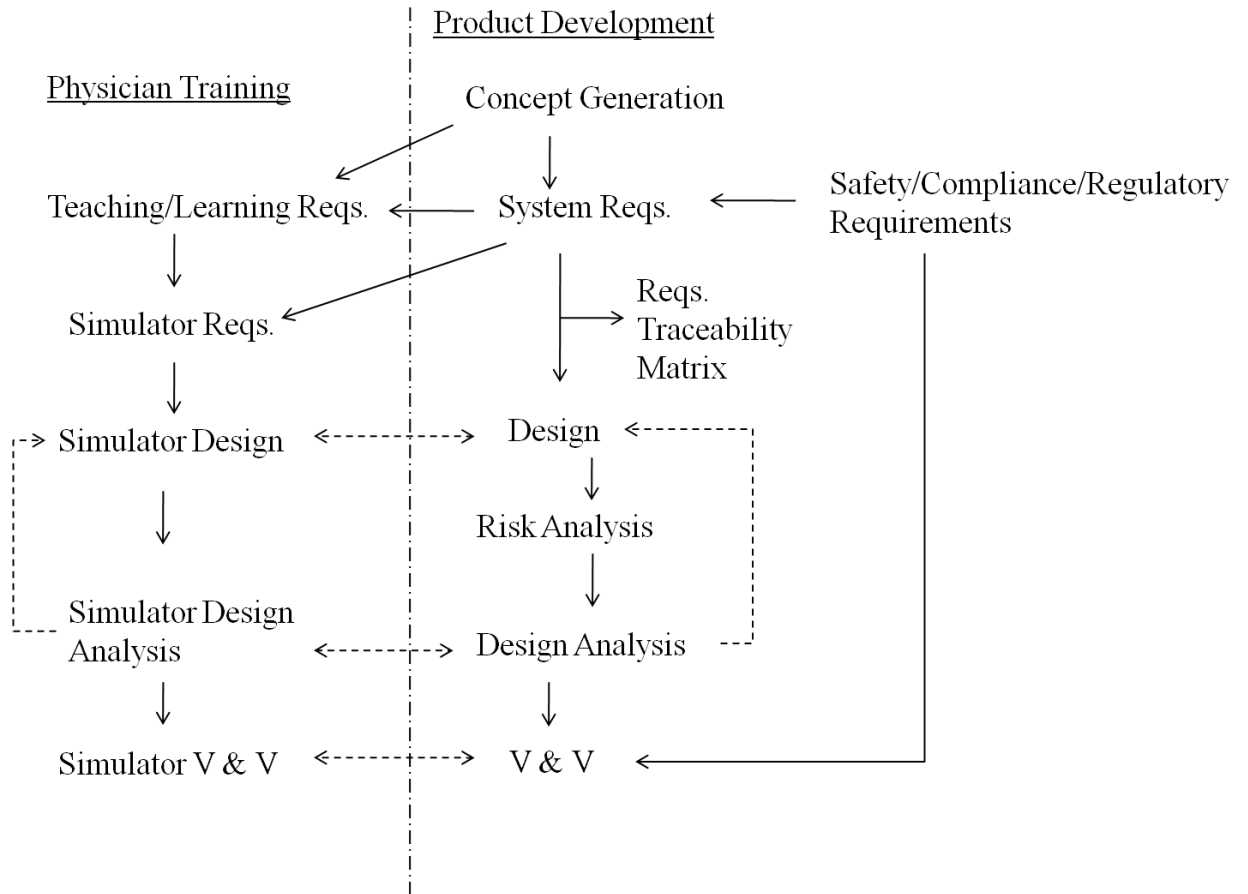


Figure 20: The Surgical Training Simulator Development Cycle extension of the Product Development Cycle (Figure 7) - repeated.

The teaching/learning requirements of the DS1000 and its associated procedure drive the simulator’s system requirements – less invasive, beating-heart mitral valve regurgitation repair. The DS1000’s Instructions For Use (IFU) and Clinical Procedure will be useful documents for this step. Imaging is performed via echocardiography; therefore, the simulator must incorporate this aspect during training.

As the design of the simulator matures, prototypes can be evaluated using the DS1000. Since validated, it is known how the device handles and reacts during the actual surgical

procedure; therefore, those reactions must match when performed in the simulator. This design analysis testing will help reveal any shortcomings in the simulator's accuracy.

Finally, a validated device (and procedure) will be well suited to validate the simulator against. As summarized from Chapter 4, evaluating users with varying experience levels performing the same task on the simulator before and after training will demonstrate 1) improvement with training regardless of experience (internal validity) and 2) that the simulator can distinguish between the experience levels (external validity). The culmination of the simulator validation will be to evaluate the same metrics, performed by the same user, on the simulator and the actual surgery (construct validity). Evaluations can include those by independent assessors or the comments from the users (surgeons) skilled in the actual procedure.

With the device's performance in actual surgery established, the final simulator must replicate this to be successful. When accomplished, the end result is a validated simulator.

CHAPTER 6- REFERENCES

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