MEDICAL DEVICE DESIGN WITHIN THE ISO13485 FRAMEWORK

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A thesis presented to the National University of Ireland Cork
for the degree of Doctor of Philosophy

January 2017

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Declaration

I hereby declare that I am the sole author of this thesis and all of the work undertaken in this thesis is original in content and was carried out by the author. Work carried out by others has been duly acknowledged in the thesis.

This is a true copy of the thesis, including any required revisions, as accepted by my examiners. The work presented has not been accepted in any previous application for a degree.

Signed: _____

Date: _____

Abstract

The design and development of medical devices has become an increasing complex and regulated process. To date, little if any consideration is given to the regulatory requirements when developing medical devices in universities. This has resulted in an imposing barrier preventing academic innovation reaching clinical adoption. The scope of universities is not to become the legal manufacturer of medical devices. However, should the development of novel devices ever aim to benefit patient care and reach a clinical setting, design controls must be implemented throughout the project life cycle to demonstrate feasibility and safety.

The aim of this thesis is to develop user-centred technologies which comply with industrial design control practices whilst helping to bolster and promote innovation within academia. Four projects relating to medical devices have been designed in response to well-defined and end-user-originated clinical needs. These devices can serve as the exemplar for the framework developed in this work with each reaching staggered phases of development within a controlled design process. Although unique, the devices have significant overlapping characteristics that lend the devices to parallel development, leveraging in-house know-how and 'lessons learned' into the process of innovation. This thesis focuses on the novelty and design of the aforementioned projects in a discrete structured approach and reflects on the development of each project within the context of a design control process which was developed as part of this work.

It is the ultimate goal of this work to develop a flexible structured system compliant with the international requirements for product design and development which may be exported internationally. However, the full execution of this ambition was limited due physical, and financial limitations. This manuscript will describe the technical and commercial opportunity of the user cantered devices and reflect on the success of developing same within a custom design control process developed as part of this work.

Acknowledgements

Undertaking a PhD has been one of the most challenging and rewarding experiences of my life so far. It has not only afforded me a fantastic learning experience, but has also led to forming close life-long friendships. The completion of this work would not have been possible if it were not for the help and support of a number of people. I would like to acknowledge and extend my eternal gratitude to the following persons who have made the completion of this thesis possible.

Firstly, I wish to thank my academic supervisor Dr Pádraig Cantillon-Murphy. It has been a real pleasure working with Pádraig over the last number of years and I have greatly learned from his vast experience of medical device design and development. I look forward to building on our friendship and working with Pádraig over the coming years to translate novel medical technologies to commercial reality. I would also like to thank Dr Bill Wright and Professor Pierre Renaud for examining my thesis.

I wish to thank the Irish Research Council for my academic scholarship and Enterprise Ireland for their financial support and advice throughout, which made this work possible. I would also like to greatly express my gratitude to the UCC Technology Transfer Office for their continued support and advice right the way through.

I wish to thank all the staff of the Department of Electrical Engineering at UCC. I would like to give particular thanks to Michael O'Shea and Timothy Power who displayed incredible skill and knowledge in fabricating prototypes in the workshop. I wish to thank Niamh O'Sullivan, Mary O'Leary, Claudia Cashman and of course Ralph O'Flaherty for their professional administrative support.

I wish to thank all the clinicians I have worked with and engaged with over the last number of years, too many to list. I would however like to give particular mention to Dr Emmet Andrews, Dr Mícheál O'Ríordáin, Dr Peter Lee, Dr Gabriella Iohom, and Dr Marcus Kennedy. Their expertise, professionalism and support has resulted in exciting new projects which I hope can be progressed for the betterment of patient health.

I wish to thank all the organisations I have worked with to progress the various projects to their current stage of development. I would like to thank Incramed Medical Device Solutions, Arrotek Medical, Arwen Consulting, Dolmen Industrial Design, and

imarc Consulting to name but a few. I would like to give particular mention to Irene Giuffrida who over the concluding months of this work, provided exceptional support in helping develop the Quality Management System.

I would also like to thank my fellow postgraduate colleagues, both past and present. Your company over the last four years created a fun and supportive environment which carefully balanced an enjoyable and productive ecosystem … mostly. Special mention goes to Kilian O'Donoghue, Diarmaid Hogan, Brendan Barry, Edward O'Dywer, Adrian O'Sullivan, Alex Jaeger, Yeny Vazquez-Guitierrez, Kevin Davis, and Robert Ryan. There were so many more I could mention, you know who you are. Thank you for all the memories, friendships and Monday night soccer.

My sincere gratitude goes to my family for helping me through my postgraduate career. To my brother Michael, my sisters Aisling and Caitriona, and my gran Nellie, thank you for all your encouragement. I would like to give special thanks to my mother, Catherine, and my father, Con, for all their love and support.

Finally, I wish to thank my fiancée Doireann. We have shared the highs and lows and you have never ceased to support me. You provided a constant source of encouragement and I could not have done it without you.

Sincerely thank you all,

Conor O'Shea

List of Achievements

This PhD balanced the technical, clinical and commercial development of novel user-centred innovation and therefore presented exciting opportunities to win financial government support and represent University College Cork at various national and international competitions and conferences. The following lists some of the most notable achievements as part of this PhD work.

COMPETITIONS

- Winner of the Global Investor Challenge (2016)
- Muster winner of the IntertradeIreland Seedcorn Competition (2016)
- Winner of the Enterprise Ireland Roots in Research Award, Belfast (2015)
- Finalist: Academic Contribution to Medtech, Irish Medical Devices Association (2015)
- Winner of the UCC Entrepreneur of the Year Awards; Most Technologically Innovative Idea (2015)
- Winner of the Boucher-Hayes Medal for Innovation in Surgery-Royal Academy of Medicine Ireland (2014)
- Top 4: MedTech Innovator IN3, Dublin (2014)
- Top 4: M2D2 New Venture Competition, Boston (2014)

FUNDING SUPPORTS AND AWARDS

Enterprise Ireland Commercialisation Awards

- SecuRetract: CF/2015/0041P

Enterprise Ireland Feasibility Awards

- SafeTrac: CF/2015-0241Y
- ProDural: Enterprise Ireland / Cleveland Clinic, Clinical Innovation Award, CCF/2013/3737Y

Academic Scholarship

- Irish Research Council scholarship, GOIPG/2013/137

List of Publications

Patents

1. **C. O'Shea**, P. Cantillon-Murphy, E. Andrews, M. O'Riordain, C. O'Donoghue, G. Burke, D. Cummins, R. Finn (2015). *Inflatable Laparoscopic Retractor for Atraumatic Retraction in Abdominal Surgery*, US Patent application No. US20150342590.
2. **C. O'Shea**, P. Cantillon-Murphy, P. Lee, J. Keane, K. Keohane, J. Delaney, P. MacSuibhne (2014) *An indication device and method for locating a natural cavity in a body*, European patent application No. 14150806.9.

Journal Papers

1. **C. O'Shea**, K. A. Khan, P. Nardelli, H. A. Jaeger, M. P. Kennedy, P. Cantillon-Murphy, "Evaluation of Endoscopically Deployed Radiopaque Tumour Models in Bronchoscopy," *Journal of Bronchology and Interventional Pulmonology*, 23(2): 112-122, 2016.
2. **C. O'Shea**, D. Kelliher, E. Andrews, M. Ó Riordáin, M. O' Shea, T. Power, P. Cantillon-Murphy, "Design, Development and Evaluation of an Inflatable Retractor for Atraumatic Retraction in Laparoscopic Colectomy," *Annals of Biomedical Engineering*, 42(9):1942-1951, 2014.

Conference Publications

1. **C. O'Shea**, K. A. Khan, J. Tugwell, M. P. Kennedy, P. Cantillon-Murphy. "The Effects of Occupying the Working Channel on Endoscopic Manipulation," *Poster presented at the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) annual meeting*, Boston, March 16 – 19, 2016.
2. **C. O'Shea**, E. Andrews, P. Cantillon-Murphy. "Appraisal of a Novel Atraumatic Retractor for Laparoscopic Surgery," *Poster presented at the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) annual meeting*, Boston, March 16 – 19, 2016.
3. **C. O'Shea**, K. A. Khan, P. Nardelli, H. A. Jaeger, M. P. Kennedy, P. Cantillon-Murphy. "Evaluation of Endoscopically Deployed Radiopaque Tumour Models in Bronchoscopy," *Irish Thoracic Society Annual Scientific Meeting*, Cork, Ireland, November 13 – 14, 2015.

4. **C. O'Shea**, J. Tugwell, K.A. Khan, M. Kennedy, P. Cantillon-Murphy. "The Impact of Instruments on Endoscopic Manipulation," *27th International Conference of the Society for Medical Innovation and Technology*, Brno, Czech Republic, September 10 – 12, 2015.
5. **C. O'Shea**, E. Andrews, M. Ó Ríordáin, P. Cantillon-Murphy. Design and development of an atraumatic retractor for laparoscopy," *Design of Medical Devices Europe*, Vienna, Austria. September 08 – 09, 2015.
6. **C. O'Shea**, P. Lee, P. Cantillon-Murphy. "Design and development of a visual syringe for epidural entry," *11th IASTED International Conference on Biomedical Engineering (BioMed 2014)*, Zurich, Switzerland, June 23 – 25, 2014.

Contributions – Journals

1. J. Tugwell, P. Brennan, J. Griffiths, T. Power, M. O'Shea, **C. O'Shea**, R. A. Cahill, K. O'Donoghue, P. Cantillon-Murph, "Electropermanent magnetic anchoring for surgery and endoscopy," *IEEE Transactions on Biomedical Engineering*, 62(3):842-848, 2015.
2. P. Nardelli, H.A Jaeger, **C. O'Shea**, K. A. Khan, M.P. Kennedy, P. Cantillon-Murphy, "Pre-clinical Validation of Virtual Bronchoscopy Using 3D Slicer," *International Journal of Computer Assisted Radiology and Surgery,* [Accepted], 2016.
3. H.A Jaeger, P. Nardelli, **C. O'Shea**, J. Tugwell, K. A. Khan, T. Power, M. O'Shea, M.P. Kennedy, P. Cantillon-Murphy, "Automated Catheter Navigation with Electromagnetic Image Guidance," *IEEE Transaction on Biomedical Engineering,* [Under Review], 2016.
4. K. A. Khan, P. Nardelli, H.A Jaeger, **C. O'Shea**, P. Cantillon-Murphy, M.P. Kennedy, "Navigational Bronchoscopy for Early Lung Cancer – A Road to Therapy", *Advances in Therapy*, 33(4): 580-596, 2016.

Contributions – Conferences

1. K. A. Khan, P. Nardelli, C. O'Shea, P. Cantillon-Murphy, and M. P. Kennedy, "The design and validation of a novel semiautomatic lung navigation platform," *in 19th WCBIP/WCBE World Congress*, Florence, Italy, 2016.

2. K. A. Khan, **C. O'Shea**, J. Tugwell, P. Cantillon-Murphy, M. P. Kennedy, "Loss of flexion of EBUS scope with needle insertion: a comparison of commercially available needles and systems." *Irish Thoracic Society Annual Scientific Meeting*, Cork, Ireland, November 13-14, 2015.
3. P. Nardelli, H.A Jaeger, **C. O'Shea**, K. A. Khan, M.P. Kennedy, P. Cantillon-Murphy, "Open-source virtual bronchoscopy in pre-clinical validation using 3D slicer", *Computer Assisted Radiology and Surgery (CARS)*, Heidelberg, 2016.
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6. P. Nardelli, K. A. Khan, A. Corvò, H. A. Jaeger, R Volpi, **C. O'Shea**, M. P. Kennedy, P. Cantillon-Murphy, "Development of a Virtual Airways Reconstruction and Navigation Platform", *Irish Thoracic Society Annual Scientific Meeting*, Cork, Ireland, November 13-14, 2015.
7. Jaeger, P. Nardelli, **C. O'Shea**, M. Kennedy, P. Cantillon-Murphy, "Bronchial Catheter Automation for the diagnosis and treatment of Lung Cancer" *Irish Thoracic Society Annual Scientific Meeting*, Cork, Ireland, November 13-14, 2015.
8. K. O'Donoghue, A. Corvó, P. Nardelli, **C. O'Shea**, K. A. Khan, M. Kennedy and P. Cantillon-Murphy, "Evaluation of a novel tracking system in a breathing lung model", *36th Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, Chicago, IL, August 26-30, 2014.
9. K. O'Donoghue, A. Corvó, P. Nardelli, **C. O'Shea**, K. A. Khan, M. Kennedy and P. Cantillon-Murphy, "Evaluation of a novel EM tracking system in a breathing lung model", *The Hamlyn Symposium on Medical Robotics*, London, UK, July 12-15, 2014.

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List of Abbreviations

ABS	Acrylonitrile Butadiene Styrene
BDRG	Biomedical Design Research Group
BOM	Bill of Materials
CE	Conformité Européenne (European Conformity)
CICV	Can't Intubate Can't Ventilate
COGS	Cost of Goods Sold
CPT	Current Procedural Terminology
CT	Computed Tomography
DDP	Design Development Plan
DFM	Design for Manufacture
DFMEA	Design Failure Mode and Effect Analysis
DHF	Design History File
DMR	Design Master Record
DRG	Diagnosis-Related Group
DTI	Difficult Tracheal Intubation
EBUS	Endobronchial Ultrasound
ED	Emergency Department
ESA	Emergency Surgical Airway
ETT	Endotracheal Tube
FDA	The Food and Drug Administration
FDM	Fused Deposition Modelling
FEA	Finite Element Analysis
FOS	Factor of Safety
ICU	Intensive Care Unit
IP	Intellectual Property
IQ	Installation Qualification
ISO	International Organisation for Standardization
LMR	Limited Market Release
LOR	Loss of Resistance
MDD	Medical Device Directive
MRS	Market Requirement Specification
OQ	Operational Qualification
PCT	The Patent Cooperation Treaty
PDPH	Post-Dural Puncture Headaches
PEG	Percutaneous Endoscopic Gastrostomy
PFMEA	Process Failure Mode and Effect Analysis
PI	Principal Investigator
PQ	Performance Qualification
QFD	Quality Function Deployment
QMS	Quality Management System
RMP	Risk Management Plan

RSI	Rapid Sequence Induction
SWOT	Strengths Weaknesses Opportunities Threats
TBNA	Transbronchial Needle Aspiration
TF	Technical File
TRIZ	Theory of Inventive Problem Solving
V&V	Verification and Validation
VL	Video Laryngoscopes

Chapter 1 Introduction

"What I admire in Columbus is not his having discovered a world, but his having gone in search for it on the faith of his own opinion." **Turgot**

Theodore Levitt once said "*creativity is thinking up new things. Innovation is doing new things*". This presents a challenge in the university setting where the main objective is to produce academic research and to invent without a clear sight to market. This becomes particularly evident in regulated markets such as medical devices. This thesis explores how adapting a linear model of device development to the academic setting may be used to bridge the gap between research and commercial innovation and demonstrates, through three novel examples, how university projects can achieve both academic merit and commercial potential. Chapter 1 presents an overview and objectives of the thesis as well as introducing the user-centred medical devices developed within the proposed framework.

1.1. Thesis Overview

This thesis explores the development of novel medical devices within a design control framework in a third level institute. To date, little if any consideration is given to the regulatory requirements when developing medical devices in universities. The implementation of product development controls can be seen as costly and burdensome. Furthermore the primary function of universities is not to become the legal manufacturer of medical products, therefore the application of standardisation during the development phase may not be seen as necessary. However, without a documented product development process to demonstrate that a device is safe, effective and meets the user needs, project outputs cannot be transferred into the clinical setting, limiting their impact on patient care and reducing their commercial attractiveness.

The aim of this thesis is to develop novel user-centred technologies which comply with industrial design control practices whilst helping to bolster and promote innovation within academia. Three projects have been incorporated into a design control process which has been adapted from the linear stage gate approach to product development [1]. The stage gate approach has been well documented [1]–[3]. However the objective of this work was to adapt the process to suit the needs of early stage research and development within the academic setting. These projects can serve as the exemplar for the adapted framework described herein. Each device (currently at staggered stages of development) is a response to a defined and end-user-originated clinical need, derived through a medical device design programme at University College Cork (UCC). The BioDesign module couples consultant clinicians with interdisciplinary student teams from medicine and engineering to solve real life clinical problems in the academic setting [4]. The UCC BioDesign module is co-ordinated by Dr Pádraig Cantillon-Murphy based on his experience at MIT and Harvard Medical School. As a follow-on from the BioDesign module, selected projects that demonstrate commercial promise are further developed within the postgraduate Biomedical Design Research Group (BDRG) at UCC where much of the work described in this thesis was completed.

An aspirational outcome of this research is to create an entity that can facilitate the future exploitation of these devices as commercially viable products. This will involve

co-operative research and development between the student, supervisor, clinical partners, business partnerships and the regulatory authorities to successfully achieve this goal. Working closely with the university Technology Transfer Office, the intellectual property surrounding each of the devices was defined and, where appropriate, protected by European patent applications.

1.2. Project Scope

The objective of designing medical technology within a controlled framework is demonstrated through the development of three novel devices, which meet well-defined clinical needs, identified by consultant-level clinicians. In the case of each device, the level of incorporation of the individual project within the development framework is varied depending on project timeline overlapping with the framework development. The resulting devices are (1) SecuRetract: an inflatable laparoscopic bowel retractor, (2) ProDural: a device to improve the accuracy of epidural administration, and (3) SafeTrac: a rapid endotracheal tube delivery device. Each of these technologies have received financial support from Enterprise Ireland. Enterprise Ireland is the government organisation responsible for the development and growth of Irish enterprises in world markets with a number of different funding supports in higher education institutes. Although unique, the three devices developed in the design control framework, have significant overlapping characteristics such as inflatable technology, disposability, similar pre-clinical pathways to clinical evaluation and suitability for IP exploitation. These similarities lend the devices to parallel development to leverage know-how and 'lessons learned' into the process of innovation. However, each device also represents a unique engineering challenge.

The author will also describe a fourth project relating the development of radiopaque tumour models which were developed outside of the design control process and will explore how one might retrospectively apply a developmental framework to this project.

1.2.1. SecuRetract

The SecuRetract project describes the design and development of a minimally-invasive retractor used during lower abdominal laparoscopic (keyhole) surgery. Current methods used to manoeuvre and manipulate impeding organs, such as the distend loops of bowel, during laparoscopic surgery present a number of adverse effects. SecuRetract aims to overcome the current difficulties with existing approaches while improving

surgical access and reducing complications. The laparoscopic retractor project represents a unique collaboration between UCC School of Engineering, the Departments of Surgery at Cork University Hospital (Dr Emmet Andrews) and the Mercy University Hospital (Dr Micheal O'Riordain), as well as a host of quality and regulatory experts (Ms Chrissie Keane - National Standards Authority of Ireland, Mr Frank Enright - IncraMed Regulatory Consultants, Ms Angela O'Sullivan - Arwen Medical Compliance).

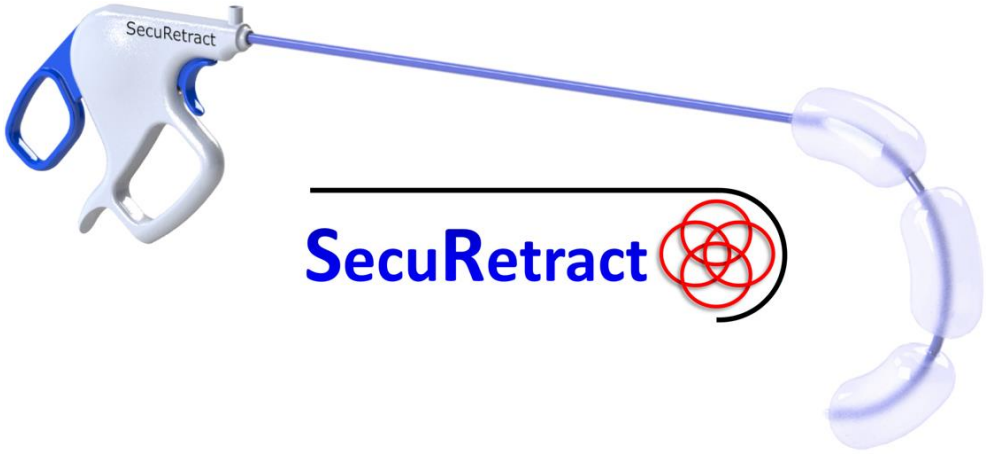


Figure 1.1 Computer render of SecuRetract, the atraumatic laparoscopic retractor, pictured in the curved and inflated position.

Published works relating to SecuRetract include a peer reviewed paper in the Annals of Biomedical Engineering describing the early stage design and utility of SecuRetract [5], as well as two conference proceedings [6], [7]. The early stage design and development of this device was included in a MEngSc thesis which the author completed before improving the design as part of this work [8]. Where overlap occurs in project timelines, clear reference shall be made to previous works.

Two Enterprise Ireland Commercialisation Awards have supported both the technical and commercial development, utilising in-house resources and external services where necessary. The design of SecuRetract has also been recognised with multiple awards to include the Enterprise Ireland Roots in Research award (2015), and the Boucher-Hayes Medal for Innovation in Surgery from the Royal Academy of Medicine Ireland (2014). SecuRetract is patent pending with filings in the USA and Europe. The SecuRetract project was developed in parallel with developing the design control framework. As a result of such, various stages of development came before the corresponding controls were in place which subsequently resulting in

retrospectively applying the design controls. A detailed review of the SecuRetract project as well as a full list of published work and awards associated with the project is listed in Chapter 3.

1.2.2. ProDural

ProDural is a device which recognises needle tip entry to the epidural space in anaesthesia, improving the ease and safety of epidural administration. Conventional means to administer epidurals during labour or therapeutic pain relief require a steep learning curve, and can result in significantly high complication rates particularly for trainee anaesthetists. The ProDural project represents a collaboration between the Department of Anaesthesia (Dr. Peter Lee) at Cork University Hospital (CUH) and the UCC School of Engineering.

Figure 1.2. ProDural concept computer render in the charged state.

ProDural has received a number of awards including winning the Enterprise Ireland/Cleveland Clinic Clinical Innovation Award (2013), Top four finish out of thirty six early-stage medical devices at the MedTech Innovator IN3 Dublin (2014), and fourth place at the M2D2 New Venture Competition Boston from fifteen globally shortlisted finalists (2014). A provisional European patent was filed for ProDural and a conference paper describing the design and development of ProDural was also published during the International Conference on Biomedical Engineering, Zurich, Switzerland [9]. Similar to the SecuRetract project, ProDural was developed in parallel to the design control process and thus aspects of the development were retrospectively captured within the framework.

1.2.3. SafeTrac

One of the most common difficulties encountered in anaesthesia is airway intubation. The problem of airway intubation particularly in patients with difficult access was presented by Dr Gabriella Iohom, consultant anaesthetist at Cork University Hospital, as part of the 2013 UCC BioDesign module. During the course of the module, a viable solution was not offered. The project was subsequently incorporated as part of this PhD work where the author re-explored the clinical need and leveraging knowledge gather from previous projects, developed SafeTrac.

SafeTrac is a single-use device providing dynamic manoeuvrability and control to improve the efficacy and safety of endotracheal intubation. SafeTrac was awarded an Enterprise Ireland Feasibility Award to assess its commercial potential in 2015. The SafeTrac project is the most recent project to be introduced through the developmental framework. As such, the early stage development of SafeTrac followed the design control roadmap despite being the least developed of the three projects.

Figure 1.3. Computer render of SafeTrac with endotracheal tube positioned on shaft ready for deployment.

1.2.4. Radiopaque Tumour Models

In addition to the three principal project briefly described above, the author has also development of a number of contrasting tumour models as part of the Biomedical Design Group's electromagnetic pulmonary navigation project [10]–[12]. The tumour models were designed for endoluminal deployment in the lung and are clearly identified under CT imagery. The purpose of the novel radiopaque tumour models is to enable effective evaluation of the navigation system through targeted sampling of identifiable fiducial makers [12], [13] (see Figure 1.4).

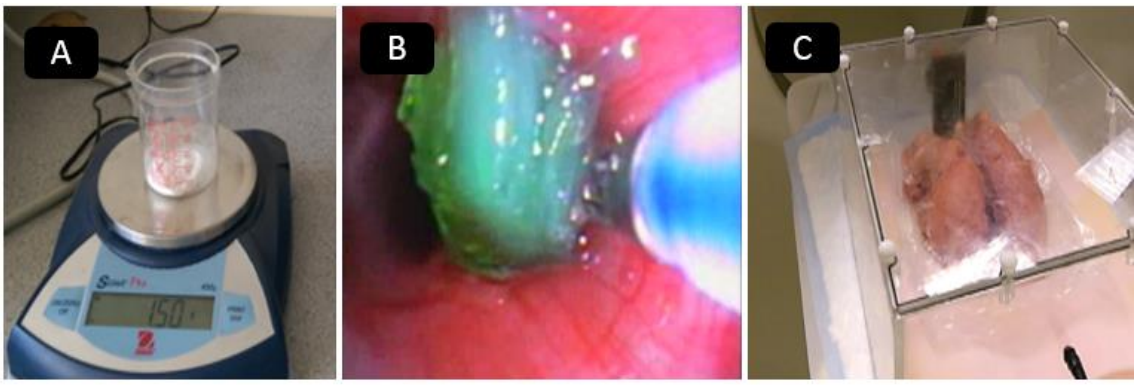


Figure 1.4 Radiopaque tumour model project images with A) the model development, B) the model *ex vivo* placement into a preserved swine lung, and C) the tumour model being scanned using computer tomography.

The tumour model project was not formally accepted as one of the projects to come under the development process as initially it was not intended for clinical or commercial output. However, since completion of this work, the author has recognised that such a model may be extensively used during systems evaluation as well as physician training. Therefore, the steps that would be required to retrospectively include a project like this one into the design control process will be discussed.

1.3. Thesis Structure

This thesis is divided in five work chapters and a conclusion chapter. The motivation behind implementing a design control framework is introduced before presenting a more detailed description of the specific research projects.

Chapter 2 outlines the design control process developed as part of this work. The aim of this chapter is not to describe in detail the complexities of regulatory compliance, but to introduce a five-phase stage-gate process of controlling the design activities to fulfil the requirements of the regulatory bodies. This chapter concludes by highlighting the importance and advantages of implementing controls not just in the industrial setting but also in the academic one.

Chapter 3 and the succeeding chapters, detail the device specific design history. These chapters focus on the novelty and origins of the device as well as the design evolution process in a logical and progressive flow. Each chapter will also relate the development of the individual project to the overall design control process. Chapter 3 deals specifically

with the SecuRetract project which is the furthest developed of the presented technologies.

Chapter 4 details the design and development activities associated with creating a solution to improving the safety and efficacy of epidural administration. The proposed solution, ProDural, provides additional confirmation that the epidural space has been reached without altering current methods of deployment.

Chapter 5 explores the development of a low cost disposable device to improve the ease of tracheal intubation. The proposed solution, SafeTrac, is at an earlier stage of development compared to the previous devices, yet a clear clinical need and commercial opportunity has been validated.

Chapter 6 details additional contributions made by the author relating the design and development of radiopaque tumour models. This work began as a response to the needs of a semi-automatic bronchoscopic navigation project being developed within the BDRG, and presents novel findings with applications in both the training and systems evaluation setting. This chapter also reflects on the feasibility or retrospectively incorporating the artificial tumour model project within a design control process.

The final chapter, Chapter 7, presents the key findings and novel contributions of the thesis, discusses the implementation of a design control process in the academic setting and proposes recommendations for future work.

Chapter 2 Design Control of Medical Devices

"For a successful technology, reality must take precedence over public relations, for Nature cannot be fooled." **Richard Feynman**

Medical device design and development is a complex process which must demonstrate that a device or system operates as intended, functions in a safe manner, and can continue to perform over a specified period of time without failure. Ensuring these requirements are met involves the careful integration of clinical needs, controlled design and development, implementation of regulatory standards and directives, and administrative controls. The design and implementation of such processes can become the determinant factor in the success of device commercialisation. This chapter introduces the concept of a quality management system for medical device design in the university setting and provides a brief overview of the design and development process being implemented within the Biomedical Design Research Group as developed through this work.

2.1. Regulatory Landscape for Medical Devices

"Primum non nocere" or "first do no harm" remains an important aphorism in medicine. Medical device design, in an aspiration to meet clinical needs and fulfil clinical utility, comes with an inherent risk to the patient and clinician particularly as device functionality becomes more complex. However, the establishment of quality systems and design controls mitigate this risk and ensure that consistent quality devices are produced. This chapter provides an overview of the regulatory requirements and outlines how an industrial process for design and development control may be adapted to the academic setting.

2.1.1. European Regulatory Pathway

In Europe, medical devices cannot be placed on the market without conforming to the strict safety requirements of the European Union. The term "medical device" covers a very wide range of products, excluding medicines, used in healthcare. CE Marking on a product declares that the product complies with the essential requirements of the European technical regulations ("Directives") related to European health legislation and is obligatory for products sold in the European Economic Area (EEA) since 1993. The three directives are:

- Active Implantable Medical Device Directive (AIMDD 90/385/EE) [14];
- Medical Device Directive (MDD 93/42/EEC) [15];
- In Vitro Diagnostic Medical Device Directive (IVDMDD 98/79/EC) [16].

These directives have since been updated to account for new and emerging trends and technology. Within the Biomedical Design Research Group, focus is exclusively given to the medical device directive 93/42/EEC with no present of future plans to branch into active implantable or *in vitro* diagnostic devices. Regulatory approval in Europe relies on notified bodies (NB) to implement regulatory control over medical devices [17] (e.g. National Standard Authority Ireland, British Standards Institute, etc.). The NB is an independent commercial organisation which is audited and monitored via the national Competent Authority (CA); a government appointed body responsible for monitoring and ensuring compliance with the provisions of the MDD. The Health Products Regulatory Authority (HPRA) is the Competent Authority in Ireland for human and veterinary medicines, and medical devices. The HPRA and NB

have the responsibility to protect the patient and end user by ensuring that medical device manufacturers meet the requirements of the relevant legislation [18].

It is the responsibility of the manufacturer to ensure that their product complies with the essential requirements of the relative legislation. For a device regarded as a medical device with an intended medical purpose, the overall steps towards achieving the CE mark are as follows [19]:

- Identify the directives and annexes that are applicable to your product;
- Classify your device and choose conformity assessment procedure;
- Implant design and quality controls and demonstrate that all the essential requirements of the legislation have been met;
- Maintain technical documentation to support compliance with requirements of the directives;
- Prepare declaration of conformity and supporting evidence;
- Submit to NB for certification;
- Register with CA (by manufacturer or an authorised representative);
- Apply CE marking on your product and/or its packaging and market product;

2.1.2. USA Regulatory Pathway

The Food and Drug Administration (FDA) is a public health agency in the United States of America who is charged with protecting consumers by enforcing The Federal Food, Drug And Cosmetic Act [20], [21]. Since 1976, the US FDA has been the responsible authority to regulate all medical devices in the United States. The goal of the FDA is to balance two competing views "the public reasonable assurances of safe and effective devices" while avoiding "overregulation" of the industry [22], [23]. To accommodate these goals, the FDA allows for two different regulatory pathways to marketing medical devices. The most common pathway is known as the 510(k) provision, which is intended to provide a less burdensome route enabling incremental technologies enter the market. A new medical device that can demonstrate "substantial equivalence" to a previously legally marketed device can be "cleared" by the FDA for marketing as long as the general and special controls, such as manufacturing, packaging, labelling and sterilisation are met. The 510(k) pathway rarely requires clinical trials, therefore approximately 99% of new medical devices in the US enter the market via this process [23].

The second regulatory pathway to market entry for new medical devices is the Premarket Approval (PMA) process. PMA submissions are similar to new drug applications in the pharmaceutical industry and require extensive testing including "valid scientific evidence" to provide reasonable assurance of safety and effectiveness [23]. The PMA process is primarily targeted towards medical devices that "support or sustain human life, are of substantial importance in preventing impairment of human health, or which present a potential, unreasonable risk of illness or injury" [24]. The Biomedical Design Research Group exclusively targets low to medium risk technologies that would fall under the 510(k) pathway as these devices present the lowest hurdles toward clinical adoption and shortest timelines to improving patient care.

2.1.3. Classification of Medical Devices

Within the legislation, medical devices are classified depending on their perceived risk. In Europe the classification of medical devices is covered by the European Directive 93/42/EEC Annex IX, and the related Irish regulation S.I. No. 252 of 1994. The task of classifying a medical device lies with the manufacturer. For medical devices, the general classification categories are outlined in Figure 2.1.

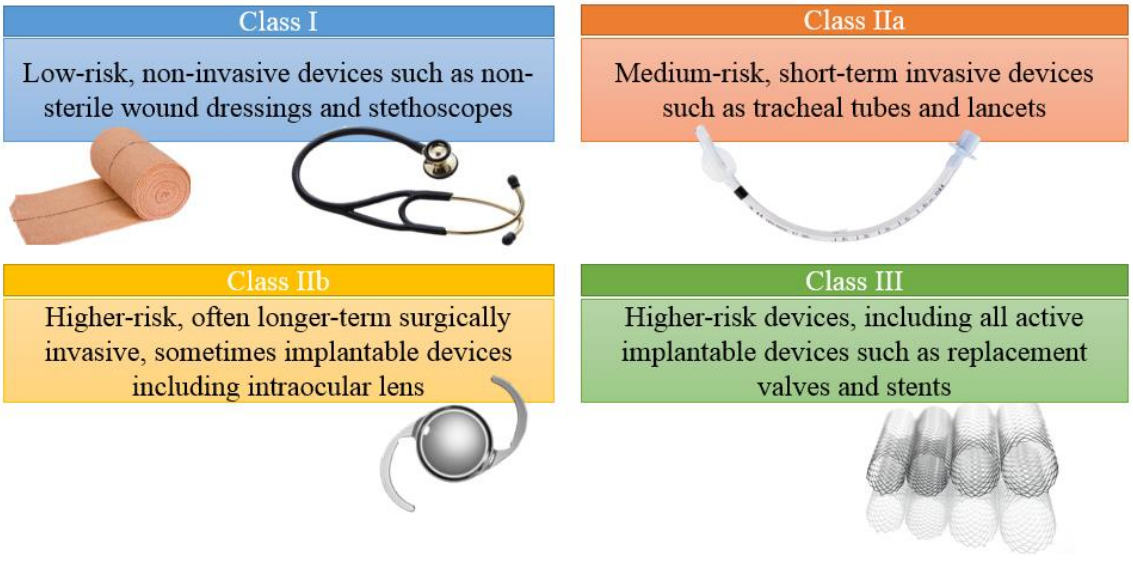


Figure 2.1 Medical device classification (MDD 93/42/EEC Annex IX)

Annex IX of the MDD provides a list of rules to direct the manufacture to the correct classification. The rules depend on the duration of contact, the degree of invasiveness, whether or not the device is active, and what part of the body is affected

by your product. The corresponding route to conformity depending on the classification of device is also described in the MDD 93/42/EEC.

In the USA, all medical devices are placed into classes based upon their degree of risk posed by the device and its intended use. The FDA also uses three classifications to differentiate the clinical risk of medical devices. Class I devices present minimal potential harm to the patient and thus are the least regulatory controlled (e.g. bandages and examination gloves). Class II devices are subjected to special controls to include special labelling requirements and post market surveillance (e.g. acupuncture needles, powered wheelchairs, infusion pumps, surgical drapes). Class III devices have the most stringent regulations and are usually those that sustain human life (e.g. implantable pacemaker, pulse generators, automated external defibrillators) [25].

The main difference between the EU and FDA methods to classification is that in the USA the manufacture does not follow rules but must find the regulation number that is associated with the product code for your device. This may be achieved by either going directly to the FDA classification database and search for a part of the device name, or, if you know the medical specialty to which your device belongs, go directly to the listing for that speciality and identify your device and the corresponding regulation [25]. FDA 510(k) reports are useful when looking at comparable devices to get an idea of the product code and corresponding classification.

2.1.4. Quality Management System Documentation

Documentation of the design control process within a Quality Management System (QMS) is mandated by both the European MDD and FDA [26]. The process for implementing a QMS for medical devices is described in ISO 13485 – Medical Devices Quality Management Systems. As part of this work, a QMS based on the requirements of the ISO 13485, with particular focus on the document control and design control activities (ISO 13485 Clause 4 & 7), has been developed. No single quality system may be applied to every organisation, however the overall structure of quality systems universally comprise of the following three levels:

Level 1: Quality Manual - The quality manual is the top level document which describes the overall quality system in accordance with the stated quality policy and ISO 13485 (see Appendix 1).

Level 2: Standard Operating Procedures - The standard operating procedures (SOP) establish the practices, procedures, policies and requirements. They are drafted from both a technical and clinical perspective and use a general format, with flow charts and diagrams as applicable. The quality manual references the applicable SOP(s). The SOP's developed as part of this work primarily focus on document and design control activities while utilising existing procurement procedures and environmental controls of the university to support supplier and human resource activities.

Level 3: Forms, Records and Specifications - Forms and records provide evidence about a past event stating results or activities performed. Laboratory notebooks, device specifications, functional characteristics, risk management reports, validation and verification protocols, packaging and sterilization processes, and manufacturing processes are all examples of records produced as part of a new product development (see Appendix 2 for an example). It is these records, specifications and reports that will be used to populate the design history of the medical device and serve as evidence to demonstrate that the design control process was implanted and that a safe and reliable solution was developed.

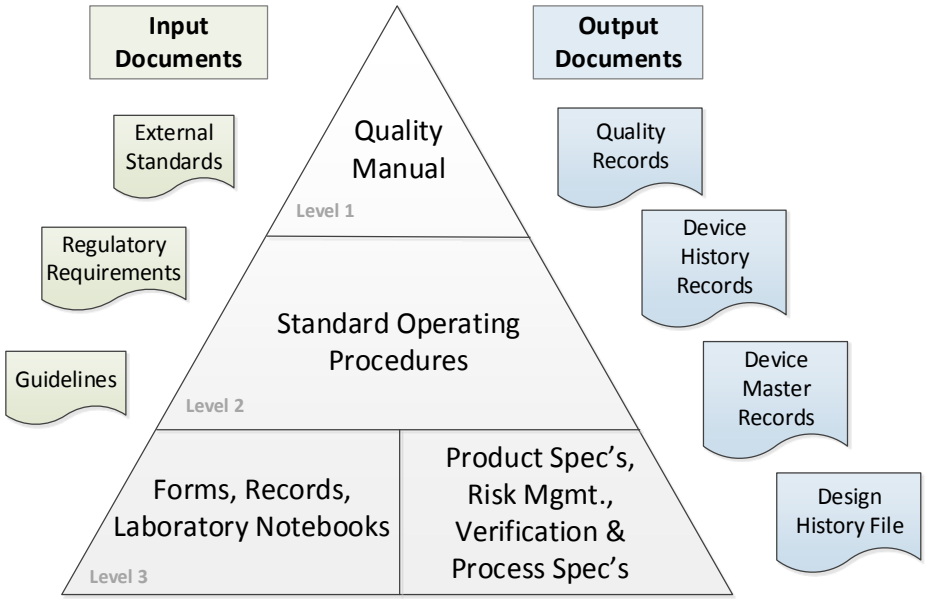


Figure 2.2 Hierarchy of documentation within a quality management system.

The complete technical documentation, declaration of conformity, the NB decisions and certificates must be kept and retained for five years (fifteen for implantable devices) after the final production of the device. These documents must also be available for presentation to the Competent Authority on request.

2.2. Design Control for Medical Device Development

Design controls are a set of quality practices and procedures incorporated into the design and development processes which are ultimately used to assure that device specifications meet user needs and intended use [20]. The design control requirements for supplying medical devices in Europe are outlined in ISO 13485 and MDD 93/42/EEC. The scope of design control applies to all Class II and Class III medical devices as well as select Class I devices (e.g. devices automated with computer software, tracheobronchial suction catheters, protective restraints). Design controls are made up of a number of elements with documented procedures that include design planning, design inputs, design outputs, design review, design verification and validation, and design changes which are captured within the QMS. Risk assessment and human factors are critical elements and should be considered at every step of the design control process. A full description of the design control elements are defined in the medical directive 93/42/EEC Annex 1, and the FDA regulations 21 CRF 820.30 [20].

2.2.1. Application of Design Control

The desire to translate university led research to clinically viable technology has been the focus of intense concern for over two decades [2], [3], [27]. A number of models have been developed to align new product development with this desire to bring ideation to market faster and more effectively [1], [3], [17], [21], [28], [29]. The design process is often represented as a simplified waterfall diagram that illustrates the iterative design, verification and validation activities (see Figure 2.3). However, this model lacks the complexities and detail required to successfully commercialise new medical technology.

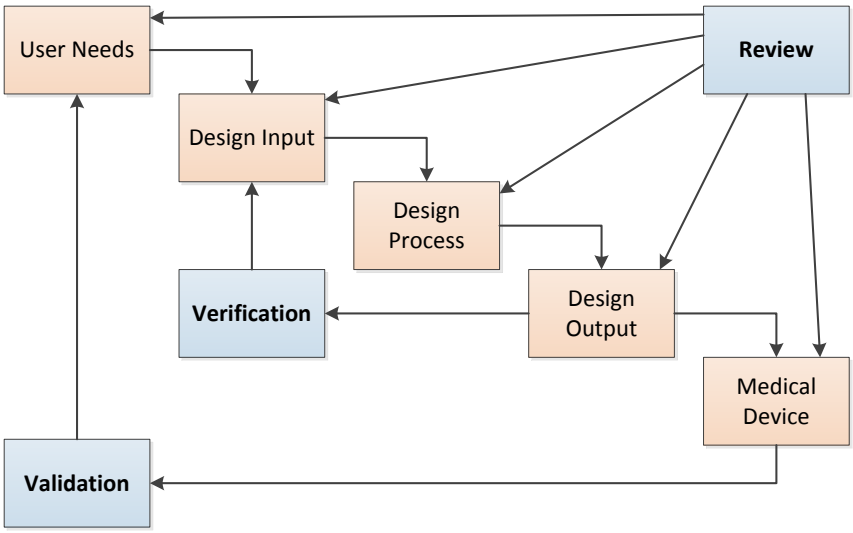


Figure 2.3 Application of design controls to waterfall design process [20]**.**

Quality function deployment (QFD) and "house of quality" methods which are well documented, aim to map the "voice of the customer" to specific plans and parameters that fulfil them [2], [26]. QFD uses matrices that include customer and technical information to build a comprehensive understanding of the patient needs. QFD can provide a partial overview of the development model and provides a clear understanding of the operational definitions and device requirements. However, QRD does not provide a complete picture of the design process and thus was not incorporated as part of this work [2].

One of the most notable process models developed is the stage-gate process [1]. Despite there not being a universally applied process to medical device design, Pietzsch *et al* (2009) carried out a systematic review of existing models and proposed a stage-gate process based on best practice with input from over 80 seasoned commercialisation and regulatory experts [2]. Pietzsch *et al* (2009) concluded that a linear stage-gate model provides a comprehensive description of the activities and outputs associated with the development process. Therefore a stage-gate model for medical device development, adapted to the academic setting from Pietzsch's high-level representation of development phases [2], was developed and expanded upon as part of this work.

2.2.2. Design Control Overview

The design control process developed as part of this work follows a linear five-phase approach to the design and development of medical devices [2]. A standard operating procedure has been developed (SOP 7.3A Design Control) to describe the design control procedure which will be further explored as part of this chapter. The phases bridge raw research with device development, beginning with initial concept generation and project approval and concluding with product release (see Figure 2.4). Although based on the development phases described by Pietzsch *et al* (2009), the author has modified the order and phase deliverables based on the experiences built up in the Biomedical Design Research Group. Furthermore, the author has broken each of the phases down into an easy to follow roadmap to focus the reader to follow a logical ordered approach to executing all the key phase deliverables.

While this chapter highlights each of the five phases of the design control process and emphasises some key associated activities, it is not the intention of universities to

manufacture and sell medical devices and therefore it is unlikely that an academic institute will progress beyond the outputs of Phase III; Design Development and Verification (i.e., a reasonable endpoint for academic projects is up to and may include clinical evaluation, without regulatory approval or commercial launch). Despite this, it is essential that academic projects with commercial merit and which aim to validate technology in a clinical investigation, comply with the essential quality requirements of the national competent authority. Furthermore if the intention is to licence the technology to a third party or to establish a spin-out entity to commercialise the invention, a QMS which accounts for product development from concept stage right through to design transfer and product launch, is essential for regulatory compliance and enhances the commercial attractiveness for partners and potential licensees.

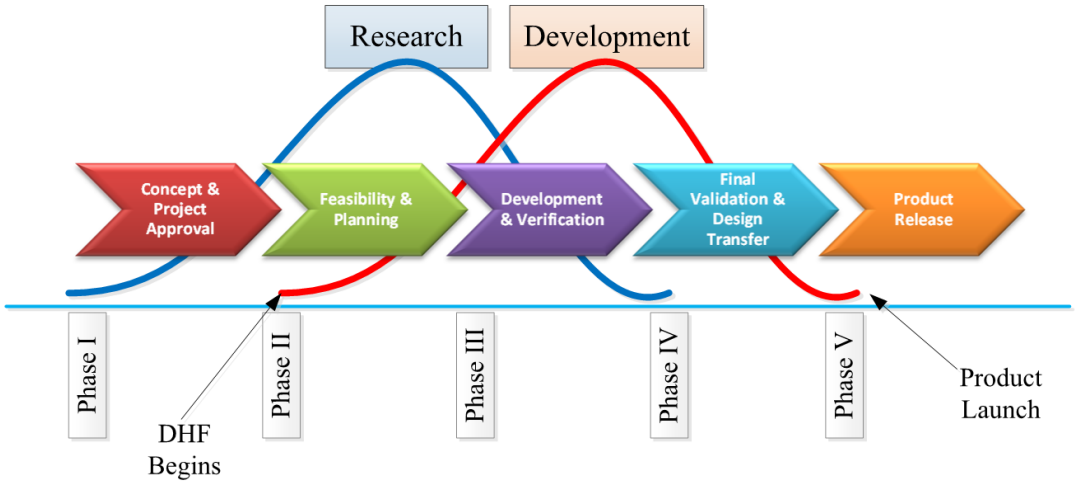


Figure 2.4 Product development process flow.

Each of the five phases illustrated in Figure 2.4 will be described in more detail in the following sections. At the completion of each phase, the design team convene to review the progress before making a decision to proceed with the activities in successive phases. However, it should be noted that although the phases are described in discrete steps, the iterative process of device development, particularly with mechanical medical devices, does not always follow this idealised linear approach, but may overlap between the phase boundaries [2]. This typically manifests itself when certain activities such as market analysis have advanced towards a later phase, while activities of the present phase may need to be repeated (e.g. prototype development). It should also be noted that despite focusing on mechanical examples of medical device development, the same phase deliverables may be applied to the application of software development. Physical requirements are replaced with software requirements specifications and robust design

and reliability testing is replaced with performance predictability and good coding practices [28]. However, for the purposes of this work, the author has focused on hardware development. The activities and phase exit decisions at the end of each phase are summarised in Table 2.1.

Table 2.1 Activities and exit decisions associated with the five-phase design control process adapted from Pietzsch *et. Al.* (2009) [2]**.**

	Phase I	Phase II	Phase III	Phase IV	Phase V
Phase Activities	**Clinical need** and problem statement definition.	Project core team selection, develop project timelines and milestones.	Translate design inputs into detailed requirements specifications, complete design for manufacturing.	Complete transfer of the design into production and produce pilot batch.	limited market release.
	R&D - Define design criteria and generate early concept solutions, early stage technical risk assessment.	Translate the defined user needs into approved design inputs.	Identify manufactures/suppliers and develop manufacturing strategy.	Complete final design validation (clinical, design, process etc.) and assure that design outputs satisfy inputs.	Initiate post-market surveillance.
	Commercial - Financial and funding requirements, market size analysis, commercial opportunity, competitive analysis, SWOT analysis.	Initiate documentation - Design Development Plan, Device Master Record, Design History File, Risk Management Plan etc.	Update risk assessment (DFMEA) and implement risk controls/mitigations.	Complete DHF, DFMEA, DMR, Technical File, process risk analysis, risk management review etc.	Sales team and physician training.
	Legal - Intellectual property (IP) landscape review	Build and evaluate early stage prototype (bench-top, animal testing, physician evaluation)	Create verification and validation (V&V) test matrix and approve testing protocols	Develop product branding, labelling and assign catalogue numbers.	Continued sales effort.
	Regulatory and Reimbursement - Early stage regulatory plan and reimbursement strategy.	Expanded IP landscape review, verify freedom to operate. [Optional: provisional patent filing]	Develop functional prototypes for V&V by end users in a simulated/pre-clinical setting [Optional: plan clinical investigation].	Finalise sales and market launch strategy. Finalise reimbursement strategy.	Continuous improvement programs and update design/process control as needed.
		Initiate risk analysis (e.g. Design Failure Mode and Effect Analysis (DFMEA)).	Create process validation plan.	Finalise manufacturing and operations launch preparation and qualification (IQ / OQ / PQ / PPQ).	Quality audits.
		Define regulatory requirements and strategy for clearance/approval.	Confirm intellectual status. [Optional: PCT Patent filing]	Complete regulatory submissions and obtain regulatory approval to market device.	
		Initiate business plan.	Update technical documents and business plan	Build product inventory / Mfg. scale up.	
Decisions at Phase Gates	There is a market opportunity.	Product design requirements are fully specified and prototype units have been approved by a physician.	Design outputs satisfy design inputs - Reached design freeze.	Validation testing shows that the device conforms to user needs and requirements.	
	The market impact is determined (i.e., disruptive vs. incremental technology).	The product offers a real value proposition which benefits the customer.	The device has an acceptable risk design risk level.	Verification testing shows that the design outputs satisfy design inputs.	
	Project risk from a regulatory, IP, technical and competitive perspective is acceptable.	The device's technical feasibility is proven and optimised.	Device can be developed from an IP perspective (i.e., no IP infringements).	Device is ready and cleared for launch, from both an IP and regulatory perspective.	
	The regulatory strategy is feasible (device classification and route to market clearance).	Manufacturing and value chain confidence has been established.	The device is ready for pilot product and final validation before regulatory submission.	Design transfer is complete - drawings to manufacturing specifications.	
	Device is ready to transfer from concept to active project status.			Process and design risk assessments are acceptable (DFMEA, PFMEA).	
				Sales/distribution partners are equipped to sell product to physicians, first customers have been identified.	
				Inventory levels are acceptable. Launch quantities are available.	

2.3. Phase I – Concept Generation and Project Approval

Phase I facilitates early stage research and concept development outside of any formal design controls and allows researchers to explore different projects at a conceptual basis before committing it to a formal design process. Phase I is also used to explore the commercial viability of a concept which critically aims to solve an end-user identified need. New projects may be presented from clinical needs identified by physicians/end users, or may come about from identifying a gap through related research and/or literature review. At the conclusion of Phase I, the project Principal Investigator (PI) makes a decision whether or not to pursue the project towards a commercial or clinical evaluation endpoint, to terminate the project, or simply to pursue the project solely as an academic research topic (see Figure 2.5).

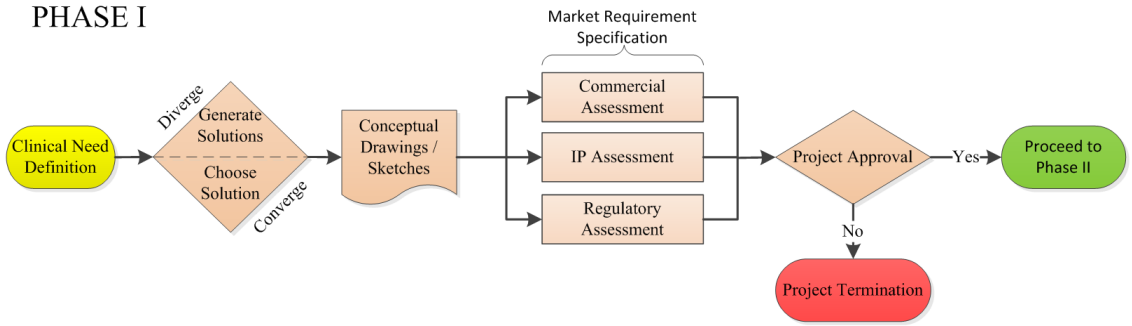


Figure 2.5. Phase I related activities and associated road map.

2.3.1. Phase I Activities

The Phase I activities, as summarised in Table 2.1, involve clearly defining the clinical need, carrying out some early stage concept generation, and evaluating the commercial opportunity.

Clinical Need Definition - Every project should begin with a clear and definite clinical need. Verification of the clinical need may involve direct observation, by speaking with clinicians, surveying end users in a clinical setting, carrying our literature reviews, engaging with patients and hands-on personnel (nurses, lab technicians), and assessing existing technologies that aim to address the clinical need [2]. Once the need has been verified, it should be summarised in a succinct problem statement. Examples of end-user identified clinical needs and problem statements will be presented in the following chapters.

Early Concept Generation - Once a clear clinical need has been defined early solution generation may begin. Typically concept generation is not addressed until the second phase of the device development process [2]. However, in this work it was found that by brainstorming and coming up with solutions at this very early stage, the inventive process is free from burdensome intellectual infringement considerations and market constraints, resulting in a much more diverse range of solutions. The number of solutions subsequently converge on review of intellectual property, competing technologies, regulations, human factors, clinical and technical risk, design manufacturability, and market constraints (e.g., manufacturing costs and potential gross margins). Clinician involvement and core group experience of potential design for manufacture considerations are key to reducing the number of solution. Tools such as TRIZ, which will be discussed in the next paragraph, may also be used to converge to a solution. Ultimately a team effort between the inventors, the Principal Investigator and the clinicians will decide on what solution should be formally introduced through the design process.

The concept generation for the projects featured in this work initially occurred as part of the UCC BioDesign module described in Chapter 1. One brain-storming technique used by the BioDesign groups is the Theory of Inventive Problem Solving (TRIZ) [4]. TRIZ was first published in 1946 by Genrich Altshuller [30] and is used extensively across many industries with increasing interest to universities [31], [32]. Altschuller realized that he could syphon the knowledge from the patent database to reduce the ideation process to a step-by-step approach based on the application and category of project scope. The TRIZ process begins with an ideation brain storming session before employing a contradiction matrix to create an array of solutions from forty inventive methods inherent to TRIZ, and finally converging on a preferred solution(s) [4], [30], [31]. The TRIZ technique towards ideation is well documented [33] and is not presented as novel in this work. However, TRIZ was employed for early concept generation of the projects described in Chapters 3-5 as part of their involvement in the BioDesign module and is proposed as a key brainstorming tool during phase 1 of the design control process.

Preliminary Market Assessment – The preliminary commercial opportunity assessment involves a top level assessment of the market size (broken down into indications of use and geography) and barriers to market entry, analysis of the

proposed solutions' strengths, weaknesses, opportunities and threats (SWOT) [34], product positioning and launch strategy (e.g. target customers, target markets, possible route to market), and determination of ideal price point to make the greatest market impact [2], [28]. A review of estimated funding requirements may also be carried out at this point. This early stage market assessment will be used to generate the basis of the business and value proposition for the product. In order to present a more succinct view of the commercial opportunity of the three devices presented in this work, Chapters 3-5 present the market opportunity unique to each device in a single section at the end of each chapter.

Preliminary Legal Assessment – Now that a solution has been proposed, the researcher can have a much more critical review of the intellectual landscape. Tools such as Google Patents[1], Patent Lens[2], European Patent Office[3] and US Patent Office[4] are useful for reviewing prior art surrounding the proposed design and intention of use. Patent law varies between jurisdictions but usually requires that, for an invention to be patentable, it must be:

- Novel (i.e., must have at least some aspect which is new)
- Non-obvious (in US patent law) or involve an inventive step (in EU patent law)
- Useful (US patent law) or be susceptible to industrial application (EU patent law [35])

Judging patentability is performed by a patent examiner on official examination of a patent application. However, on completion of the prior art review, an opinion can be sought from an IP attorney before filing a provisional patent to secure the proprietary filing date on the disclosure. King and Fries (2009) describe the complete patent process in more detail while also elaborating on other forms of legal protection including copyright and trademarks [26].

On review of the prior art, design changes may be required to avoid potential infringements. An example of when design modifications were required can be seen during the design evolution of ProDrual, where the original BioDesign concept was changed on recognition of possible IP infringements as part of this work (see Chapter 4).

[1] www.google.com/patents
[2] www.lens.org
[3] www.epo.org
[4] http://www.uspto.gov/patents-application-process/search-patents

If on further examination it is found that the team cannot overcome core claims of a competing patent but would like to pursue a solution with clear benefits and additional functionality over an infringement, it is still possible to acquire the licence for the patent in question downstream provided the resources are available and the justification is compelling. However, in practice, higher level institutional funding is often sourced from government state aid bodies and the technology development is protected by the appointed Technology Transfer Office (TTO) of the institute. Neither the funding bodies nor the TTO would be inclined to support a project without clear sight to clean IP protection. Therefore, novelty and freedom to operate often decides the continuation of research projects in the university setting.

Preliminary Regulatory Assessment- The purpose of a regulatory assessment is to identify the regulatory pathway for market approval in both Europe and the USA. As described in Section 2.1, the EU and the USA require different approaches towards market approval and device classification. Once the device description and intended use are defined, the FDA 510(k) premarket notification database may be used to identify the FDA product code applicable to the device. For example, in the case of SafeTrac, the FDA product code BSR and corresponding regulation number 868.5790 for tracheal tube stylets, would indicate that SafeTrac may be classed as a Class 1 device (see Chapter 5). Once the device has been classified, the route to FDA clearance is determined (e.g. 510(k) or PMA).

In Europe the Medical Device Directive (MDD) 93/42/EEC Annex IX classifies devices as Class I, IIa, IIb and III. In the case of SafeTrac, an invasive device for transient use, the device is Class I in accordance with Rule 5. Depending on the device classification, the MDD then outlines the route to CE conformance.

Market Requirement Specification (MRS) – The MRS compiles the results of the clinical need definition, concept solution and intended use, market analysis, regulatory pathway and legal review. The MRS is presented to the project Principal Investigator who will make a decision of whether or not to formally pursue the project (i.e., proceed to Phase II) based on whether or not a viable solution has been presented with a clear market opportunity and acceptable risk and regulatory assessment (see Table 2.1). The content of the MRS may also be used to source funding to support the next phase of project development. In the case of the SafeTrac project, the MRS was

used to secure an Enterprise Ireland Feasibility award to develop the commercial opportunity as well as engaging with a number of esteemed key-opinion leaders for clinical feedback (see Chapter 5).

2.4. Phase II – Feasibility and Project Planning

Phase II begins once a project is committed to the quality management system and designates a formal "start date" of design controls. Phase II, which is entitled Feasibility and Project Planning, is concerned with initiating design records, developing a plan for product development, and evaluating design prototypes for technical feasibility with continuous feedback from one or more clinical mentors (see Figure 2.6).

2.4.1. Phase II Activities

The first activity in Phase II, as listed in Table 2.1, involves selecting a core team and setting out general project timelines and goals. The team selection will depend on the complexity of project and financial resources but should at least comprise of one or more researchers (typically a final year undergraduate or postgraduate student), a Principal Investigator (supervising lecturer), and a clinical mentor. It is imperative to success that the team should possess multifunctional skills and capabilities, have a common purpose, engage in regular communication with shared resources, and draw on outside expertise and resources as required. The composition of the team, project timelines and key milestones are outlined in a Design and Development Plan. Once formed, the team should begin to document design activities through initiation of design records such as the Design History File which will be continuously updated until final production and market launch.

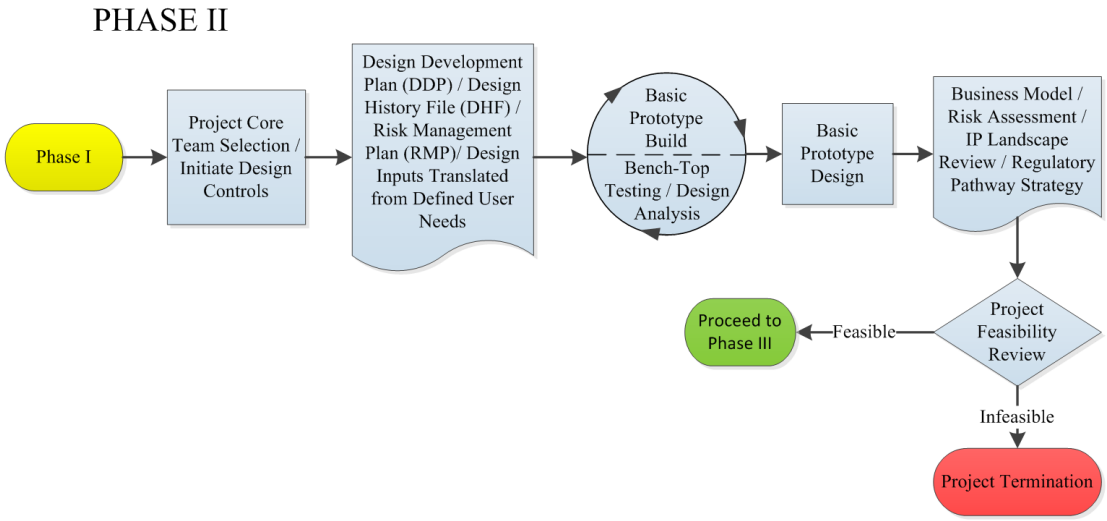


Figure 2.6 Phase II activities and associated roadmap.

Design History File (DHF) – During Phase II, the DHF will be initiated. The DHF is mandated by both the FDA and MDD and contains or references the records necessary to demonstrate that the device was designed and developed in accordance with the approved design plan and the regulatory requirements. A check list for the design file is available in Appendix 3. The completed DHF may include the following:

- Detailed design and development plan specifying design tasks and deliverables as a "living document," usually in several iterations;
- Copies of approved design input documents and design output documents;
- Documentation of design reviews;
- Verification and validation documentation; and
- Copies of controlled design documents and change control rationale and records, when applicable.

The outputs from the DHF are the **Technical File** (TF) (or Design Dossier for Class III devices) which is required for CE Marking (MDD 93/42/EEC), and the **Design Master Record** (DMR) as mandated by the FDA (see Figure 2.7). Both the DMR and TF contain all of the device specifications and procedures necessary to manufacture the final product with elements from the DHF. They also demonstrate compliance with the list MDD Essential Requirements (for that product), and the company's "Declaration of Conformity" for that product [20], [36] (see Appendix 2). SOPs 7.3B and 7.3C developed as part of this work describe the requirements for the DHF and TF respectively.

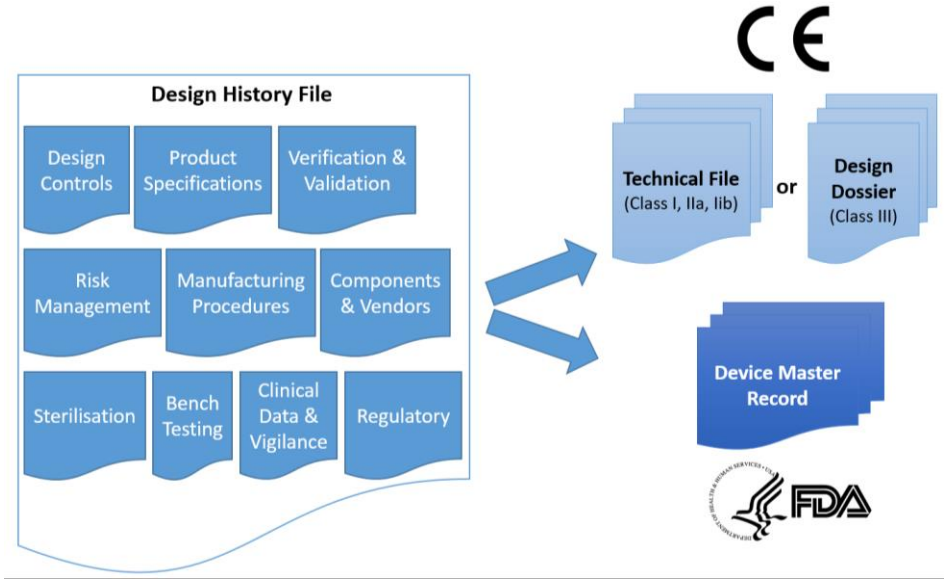


Figure 2.7 Example of records contained within the design history file and its associated market specific outputs.

Design and Development Plan (DDP) – One of the first documents produced as part of Phase II is the DDP which will be located in the DHF. Design plans describe or reference design and development activities and define responsibility for implementation. The DDP may contain Gantt Charts, defined milestones, tasks, timelines and responsibilities. The DDP will refer to key elements of design control such as defining design inputs and design outputs, carrying out design reviews, and initiating risk management activities. The DDP will also outline a plan for design verification and design validation. However these activities will not take place until later phases [20]. The plan is a working document that may be updated as the project progresses.

Design Input – Inputs define the physical and performance requirements of a device to be designed. The design input requirements are generated from the clinical needs and the intended use as described in Phase I, as well as meeting the requirements of any applicable standards mandated in the market(s) in which the product may be used.

Design Output - Design outputs are used to evaluate the device's conformance to design input requirements. Design outputs describe the acceptance criteria and identify the critical performance and safety criteria essential for the proper functionality. Outputs are confirmed by verification and validation activities which will be discussed in later sections. For example, in the SecuRetract project, a design output may be the measured burst rating of the modular balloons which fit within the limitations of the design input requirements.

Design Reviews - Formal documented reviews of the design results are to be planned and conducted at appropriate stages of the device's development (e.g., at the end of each phase as well as on a regular continuous basis). Design review participants can include outside representatives who may provide expertise or input regarding the phase of design (e.g., clinical mentor during reviews involving decisions critical to end-user experience). An individual(s), who does not have direct responsibility for device design is also required during formal design reviews as an independent "voice" [36].

Risk Management Plan (RMP) – Risk management should also be initiated during Phase II. The design, production and use of a medical device inherently entails some degree of risk. The objective of risk management, as described in the ISO 14971 – Medical Devices Application of Risk Management, is to minimise use-related hazards, and to assure that end-users are able to use the medical devices safely and effectively

throughout the product life cycle. The overall process to risk management is described in the SOP 7.1 Risk Management, based on the requirements of ISO 14971 (see Figure 2.8).

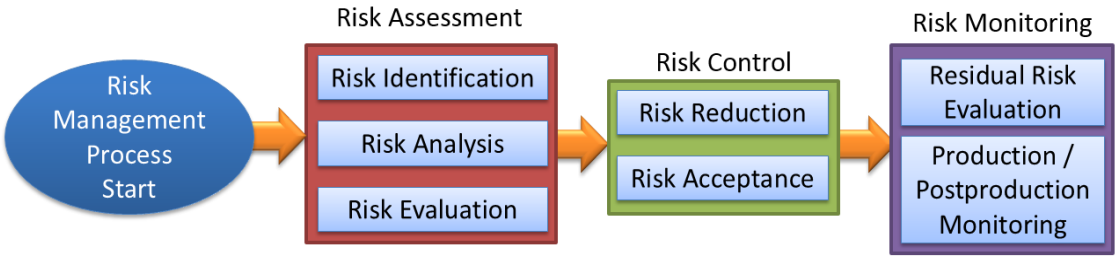


Figure 2.8 Risk management process overview.

A tool used by the Biomedical Design Research Group to identify, analyse, evaluate and control risk is Design Failure Mode and Effect Analysis (DFMEA). DFMEA is a well-established step-by-step approach for identifying all possible risks of failure in a design process and scoring the risk based on the potential severity of the adverse event and the likelihood of occurrence (see Figure 2.9). DFMEA is also used in the product design development, as risk identification outputs are used as design inputs. The DFMEA as described in SOP 7.1 developed as part of this work, grades both the severity and occurrence out of five where a score of five would indicate a life threatening injury on the severity scale and a score of one would indicate negligible or no adverse health consequences. A partial example of a DFMEA as completed for the ProDural project may be seen in Appendix 4.

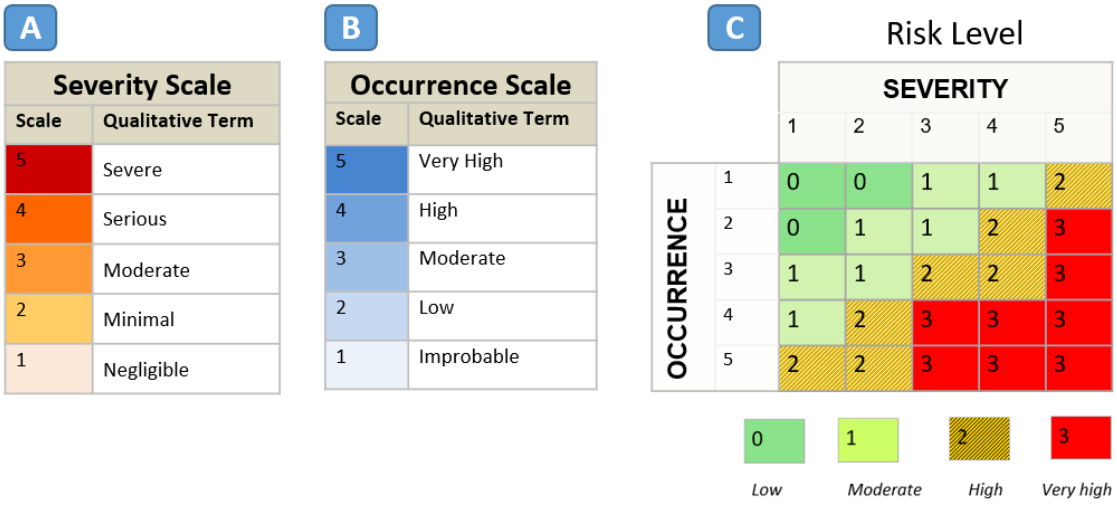


Figure 2.9 Simplified qualitative version of the severity and occurrence scale (A, B) used by the BDRG to assess the risk level (C) of a potential hazard.

Prototype Build and Assessment – Once all the controls have been established, further design development can proceed utilising the design inputs and risk assessment outputs as described earlier. The following chapters will focus on the design development and prototype testing through an iterative design process with continuous feedback from clinicians. The majority of the design development and testing activities presented in Chapters 3-5 were carried out during Phase II of the respective projects. The object of the testing in this phase, which typically involves physical bench-top and simulated evaluations (optional: pre-clinical investigations), is to demonstrate proof of concept and to establish technical feasibility. These tests provide confidence to the project team that the proposed solution performs as intended before investing in production quality models to carry out design verification and validation activities as will be described in later sections.

Business Proposal Update – Phase II will also involve more in-depth research into the overall value proposition from a commercial, IP, and regulatory perspective continuing from Phase I. This updated review, along with demonstrating technical feasibility, may be combined in order to apply for further financial support to continue the developmental process. In Ireland, the Enterprise Ireland Commercialisation award is ideally suited to support R&D activities as well as achieving commercial milestones for higher level institute research projects with real commercial promise and intent. The SecuRetract leveraged this source of funding to support its ongoing development over the course of this PhD program (see Chapter 3).

At the conclusion of Phase II, the Principal Investigator and project team will make a determination on whether or not to proceed to the next phase of project development whilst considering the phase gate decisions as listed in Table 2.1.

2.5. Phase III – Design Development and Verification

Phase III defines the activities and outputs associated with the design development and verification phase. Phase III takes the basic prototypes from the previous phase and refines same to comply with design for manufacture (DFM). This would normally involve a level of engagement with a third party supplier or manufacturer to ensure industrial compliance. The final device function, performance and safety requirements will be specified and the regulatory, commercial and clinical activates will be fully defined (see Figure 2.10). Whilst DFM is discretely addressed in Phase III, it is in fact considered

throughout the design and development process. The final DFM in phase 3 comes after functional prototypes have been evaluated in a simulated or clinical setting thus confirming that the design meets the user needs. Biocompatible materials should already have been identified and the changes if any are required should simply accommodate the manufacturing process or improve the manufacturing process (reduce parts, reduce complexity, modify drafts, etc.) while not changing the overall functionality of the device. Once the DFM is complete the device has reached design freeze and any future design changes are subject to formal change control.

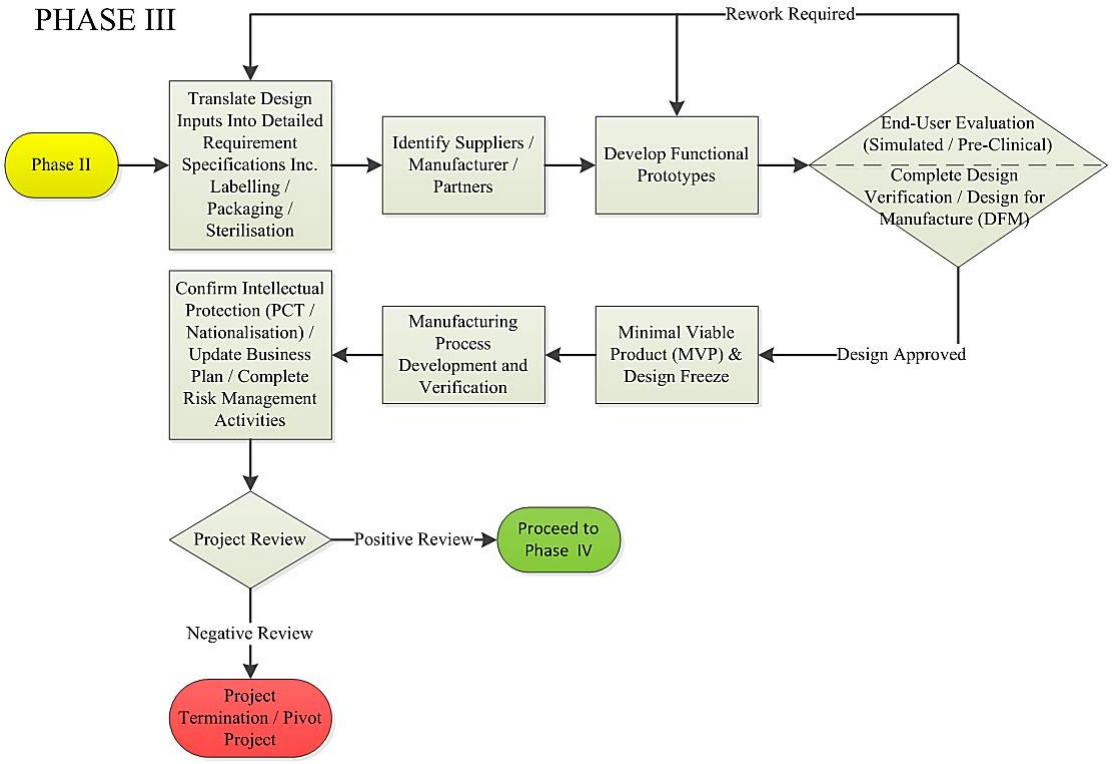


Figure 2.10 Phase III activities and associated roadmap.

2.5.1. Phase III Activities

The principal R&D activity during Phase III involves translating the design inputs into detailed requirement specifications including labelling and packaging specifications and reaching design freeze. Design freeze denotes that point at which the team formally approves a design and any further design changes will have to undergo design change controls. Prior to approval of design freeze, functional prototypes are produced working with qualified suppliers and design verification is carried out. Design validation activities may occur during this phase (e.g. if the functional prototypes are equivalent to final production product standards), but typically occurs in Phase IV as discussed in Section 2.6.1.

Design Verification - Design verification confirms that the specified requirements are fulfilled (i.e., design outputs meet design inputs). Design testing to demonstrate technical feasibility can involve simulated and physical experimentation of prototypes during the design iteration process. However, formal design verification for clinical or regulatory approval must be performed on products as close to final production as possible. In other words, the legal manufacturer (i.e., the licenced company who aims to commercialise the device), must demonstrate the prototype/product used during design verification is substantially equivalent in material, functionality, and performance as well as similar methods of packaging/labelling and sterilisation to the final product which will be placed on the market. Verification may involve biocompatibility, sterility, functional testing, packaging / shaking / dropping / shipping and accelerated ageing studies. Electronic products have their own series of tests required by various standards for safety, electromagnetic compatibility (emitting and receiving) and similar [36].

Design Changes – Once a design has been formally approved by the PI and team, a design control system must be implemented to control any further modifications to the verified design. There are the two principal administrative elements of controlling of design changes:

- **Document control -** involves tracking documents associated with the design and listing their status in the revision history. These documents refer to all design records, drawings, and specifications which characterise the design.
- **Design control -** involves recording deficiencies and corrective actions that arise from verification and review of the design and tracking their resolution prior to design transfer.

Both of these elements are documented in the device's Design History File.

The complete list of activities conducted during Phase III are itemised in Table 2.1. Many of these activities involve updating project records from Phase II (e.g. DDP, RMP, DHF, and Business Plan). During Phase III, the team may opt to further their IP position by filing a PCT application. The Patent Cooperation Treaty (PCT) provides international patent protection by simultaneously seeking protection for an invention in 148 countries throughout the world. Subsequent market specific patents may be required (i.e. patent nationalisation).

The decisions at the phase gate are listed in Table 2.1 and mainly focus on whether or not the presented design is ready for pilot production and final validation from an IP, business and technical risk perspective.

2.6. Phase IV – Final Validation and Design Transfer

Phase IV relates to final product validation which essentially provides the evidence required for full product launch. Typically this phase involves validation of the device in a clinical setting. The final pre-launch activities such as obtaining regulatory approval, finalising reimbursement plan [37], go-to-market strategies, and full process qualification will also be carried out during this phase (see Figure 2.11). As discussed in Section 2.2, it is unlikely that university projects progress into Phase IV as the activities therein are more associated with manufacturing and clinical validations. However, certain projects, particularly software related with less onerous validation criteria and investment requirements, may proceed to Phase IV.

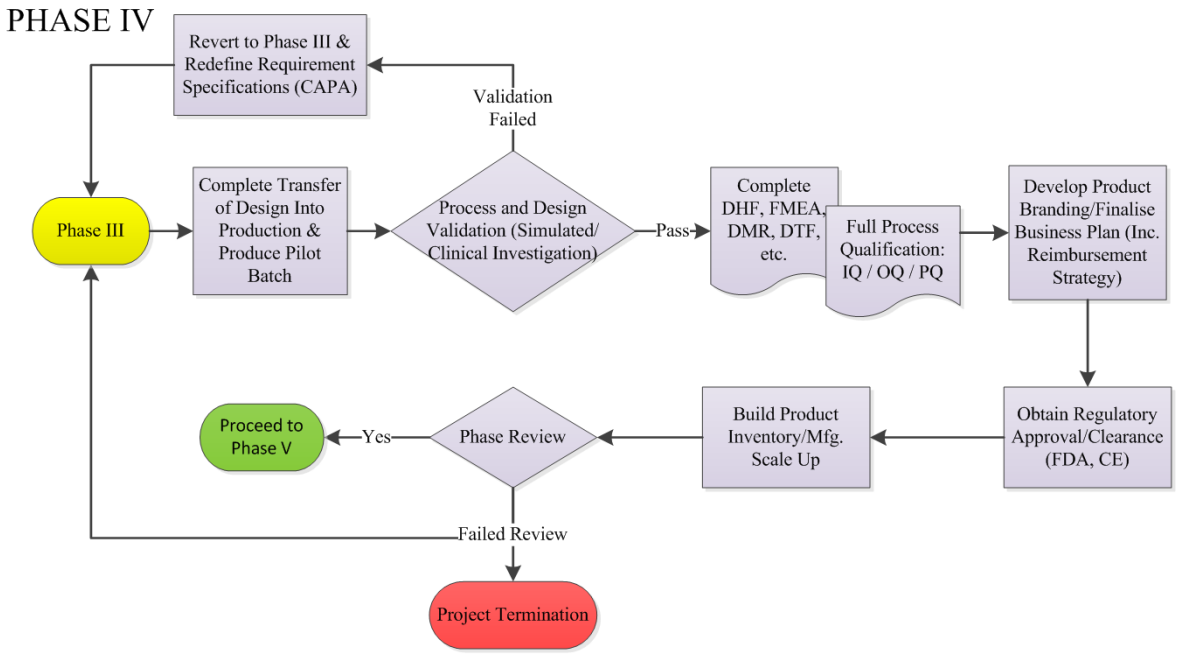


Figure 2.11 Phase IV activities and associated roadmap.

2.6.1. Phase IV Activities

The enumeration of activities associated with Phase IV are listed in Table 2.1. These activities focus on final preparation of the device for market launch and involve completing final design and process validation, closing out the Design History File, acquiring regulatory clearance and finalising sales strategy.

Design Validation - Design validation confirms by examination and provision of objective evidence that the device conforms to user needs and intended use. Design validation is to be performed on pilot production units, lots, batches or any of their equivalents under defined operating conditions (use of early stage prototypes are to be avoided since this weakens the validation purpose). Validation will include testing of production units under actual (clinical) or simulated use conditions, with such products having been fabricated in a certified production environment. Failure to comply with validation requirements can result in future product recalls [36]. SOP 7.3F Design Verification and Validation developed as part of this work outlines the procedure for verification and validation activities.

Design transfer – Design transfer is the collective set of activities conducted to transfer the device from R&D to manufacturing. The transfer activities ensure that the functional specifications of the device are properly transferred into production specification. The activities confirm that the device manufacturing process is repeatable and produces units that are safe and effective for their intended use.

Regulatory Submission – As described in Sections 2.1, different routes are required for regulatory approval depending on the intended market of sale. For both CE Marking and FDA approval, documents must be compiled that define the final product. The Technical File (CE) and Device Master Record (FDA) detail for that product [36]:

- General Information / Product Description / EC Authorized Representative,
- Classification Determination (93/42/EEC Annex IX [select applicable rule]),
- Essential Requirements (93/42/EEC Annex I),
- Risk Analysis,
- Product and labelling Specifications,
- Design Control,
- Clinical Evaluation (93/42/EEC Annex X),
- System Test Reports / Functional Bench Testing,
- Lab Testing (e.g., cytotoxic, haemolysis, sensitization, biocompatibility testing),
- Sterilization validation and Packaging Qualifications,
- Manufacturing process and qualification,
- Declaration of Conformity (93/42/EEC Annex II, V, VII),
- Appendices (further supporting information / details on the above).

Once all validation and design transfer activities are completed, and the device has been cleared for launch from both a regulatory and IP perspective, the project may now proceed to the final phase associated with market launch.

2.7. Phase V – Product Release

The final phase, Phase V, concerns product launch and continuous post launch surveillance to measure and maintain quality and regulatory compliance (see Figure 2.12). This phase signals the end of the R&D activities for a product and focuses on commercialisation and unit sales. None of the devices discussed in this thesis have progressed to Phase V.

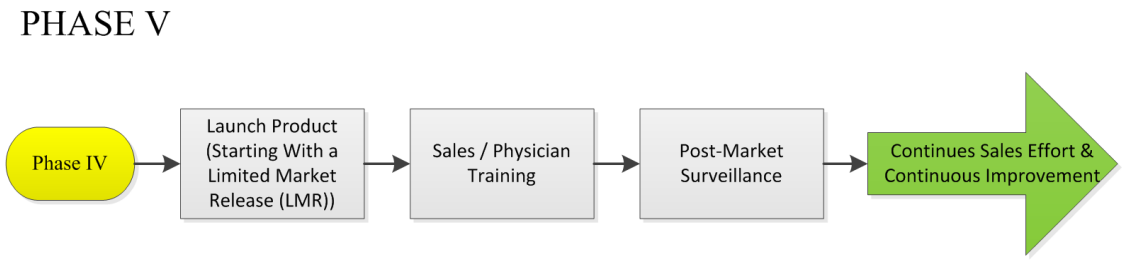


Figure 2.12 Phase V activities and associated roadmap.

2.7.1. Phase V Activities

The activities related to the final phase of the design control process are listed in Table 2.1. Product release typically would involve a phased approach starting with a limited market release (LMR) to target high-volume medical centres to obtain early market feedback from end users, as well as securing distribution partnerships. However, these relationships should have already been formed during Phase IV. Other product release activities include physician training, continued sales effort, continuous improvement programs and implementing post market surveillance.

Post-market surveillance - Surveillance must be implemented and maintained through collection of quality, safety and performance information to evaluate any potential or early signs of unexpected results for marketed products. This includes, but is not limited to, risk assessment, customer surveys, legal feedback, complaint history, clinical data, internal auditing or regulatory actions. Post launch changes to a released device design may adversely affect its safety or performance and therefore an adequate impact assessment and a review of the design changes is required to ensure that all proposed changes do not affect the product safety and efficacy. All

changes to the design or production of a marketed device must be notified to the regulatory authorities for approval.

2.8. Design Control Summary and Implementation

Industrial quality management systems and linear stage-gate models for medical device design control have been extensively discussed in literature [1]–[3], [17], [26]–[28]. However, no one system can be applied across all sectors and applications. Therefore a unique QMS with SOPs and template records has been developed to suit the needs of the Biomedical Design research group. This chapter briefly outlines the design control process being implemented at the UCC BDRG as developed as part of this work.

The five-phase process described herein takes the conventional high level development process [2], [3] and expands on each phase through the development of milestone orientation flow charts. The nuances of the presented process include an earlier emphasis on concept generation to facilitate student ideation prior to development activities, utilising institutional procurement processes for supplier management to offset approved vendor requirements, exploiting external funding to support prototype and business development and leveraging in-house resources and expertise to expedite fabrication and verification activities. However, academic led research can only go so far within the confined scope of practice of the institution. Therefore, to fully execute the design control process to design transfer and product release, a licencing agreement to a spin-out entity or established strategic partner will be required. That said, having the systems and procedures in place to fulfil the regulatory requirements, reduces the gap between stand-alone academic research and industrial application, and serves to heighten the commercial prospect and attractiveness of university led research. Furthermore a controlled system lends a structured roadmap to expedite project development and provide structure to academic researcher.

This chapter also illustrates the importance of implementing such processes and systems in the highly regulated medical device sector. The implications of not introducing design controls has been analysed by the FDA (64 FR 52605, October 07, 1996) who found that preceding the introduction of design control requirements, 44% of the quality problems that led to voluntary recall actions between October 1983 and September 1989 were attributed to errors of faults designed into the particular device which may have been prevented by adequate design controls [38].

Currently several of the document control and design control procedures have been issued and are being implemented through device design development. However, as the SOPs are being implemented, the author and team are discovering new ways to improve the procedures to reduce the workload and improve compliance. It is the overall goal of the BDRG to share a tried and proven QMS, appropriate to the requirements of the university setting and which comply with the regulatory requirements for design control, with the wider academic community. This will require introducing complete projects through the system and receiving independent review of the controls before an effective system may be disseminated.

Three projects, SecuRetract, ProDural and SafeTrac, were developed in so far as possible, within the design control process as outlined in this chapter. Each of these projects originated from end-user defined clinical needs as part of the UCC BioDesign Module with commercial potential from the beginning. It should be noted that as a result of building the quality management system, and developing the design projects in parallel as part of this work, some of the developmental activities were completed before the corresponding controls were established. However, at all points throughout the projects, careful notes were retained and dated, archiving all the key design milestones. The current phase of developed of each of the project is illustrated in Figure 2.13.

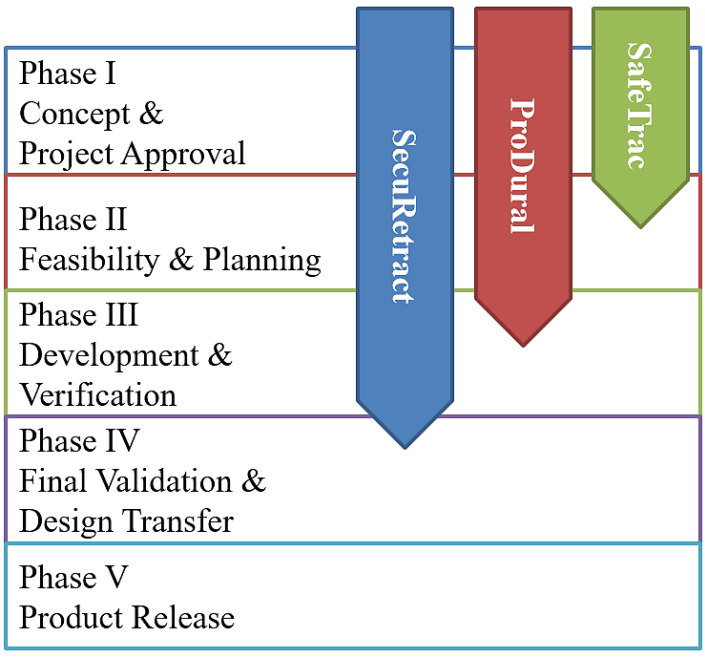


Figure 2.13 Current phase of development of the three projects developed within the design control process.

In the interest of continuity of thought and ease of presentation, the three projects discussed in the following chapters follow a logical progression from their respective clinical need definition to their current stage of development and commercial opportunity, with an emphasis on novelty, design evolution, prototype development, and evaluation techniques. At the conclusion of each chapter, a reflection will be made to consider the project's development within the controlled framework and will discuss the benefits and disadvantages of the proposed design control process.

Chapter 3 SecuRetract: an Atraumatic Inflatable Laparoscopic Retractor

One of the most common frustrations and complications in laparoscopic (“keyhole”) surgery is the seven meter long bowel migrating around the abdominal cavity and obstructing the surgical field of view. Thus the surgeon is prevented from carrying out the procedure. This problem is evident in all lower abdomen laparoscopic surgeries but is of particular concern in colorectal and hysterectomy procedures where the bowel is especially obstructive. This chapter explores the design and development of novel surgical instrument designed to effectively engage and retract the impeding bowel from the surgical space during laparoscopic surgery.

3.1. Background and Clinical Need

The retractor project arose when two consultant colorectal surgeons, Dr Emmet Andrews (Cork University Hospital) and Dr Mícheál O'Ríordáin (Mercy University Hospital), independently proposed the challenge of small bowel retraction to an interdisciplinary team of engineering and medical students during the 2012 UCC BioDesign Module. Following an Enterprise Ireland commercialisation award, the project formed the subject of an MEngSc thesis by research which the author completed in 2013 prior to commencement of this PhD research [8]. During the MEngSc research, the original concept was redesigned and developed to a functional prototype which was then evaluated in a pre-clinical study. As a result of the study outcomes, the author continued to develop and to refine the design as part of this PhD research, within a controlled design framework, and while working closely with professional services to achieve a design fit for manufacture. This chapter will examine in more detail the unmet clinical need for bowel retraction in lower abdominal laparoscopic surgery, and will outline the work undertaken during this project to address the need, describing the design process from concept to current design.

3.1.1. Laparoscopic Surgery

Laparoscopic (keyhole) surgery was first introduced in 1991 and has quickly become the gold standard in minimally invasive clinical interventions [39]. The short term benefits of laparoscopic surgery include reduced hospital stay, less postoperative pain, earlier return to normal activity, improved cosmesis, and overall reduction in health-care costs [40]–[42]. Lower abdominal laparoscopic surgery, such as colon or uterine resection, is performed with the patient under general anaesthesia. Once a pneumoperitoneum (abnormal presence of air or other gas in the peritoneal cavity) has been established to 12 to 15 mm Hg with CO_2 [43], a number of surgical cannulas (trocars) are inserted through the abdominal wall to provide surgical access. In order to ensure a clear line of sight, surgeons need to remove impeding organs such as the distended loops of bowel from the operating view [44]. The most common method used to retract the bowel involves placing the patient in a steep head-down position known as the Trendelenburg position (TP) and using bowel graspers to manipulate the bowel [45]. TP involves inclination of the patient's body with his or her head down and legs elevated. To optimise surgical exposure, an angle of inclination greater than

40° may be required for several hours [45]. This allows the small bowel to glide away from the pelvis, creating a working space within the abdominal cavity, which in turn allows the surgeon to mobilise the target lesion and retrieve the specimen extracorporeally through an enlarged port site. Post anastomosis, the bowel is returned into the peritoneal cavity, and the facial defect (incision from instrument port) is closed [46].

3.1.2. Bowel Retraction Techniques

Manoeuvring the seven meter long distended bowel provides one of the most common challenges encountered during laparoscopy [44]. By placing the patient in the TP, the surgeon uses gravity to retract the bowel (see Figure 3.1 A). However, prolonged TP significantly increases intracranial pressure and intraocular pressure due to increased venous pressure [47]. In addition to the circulatory effects, steep head-down impacts on both the cardiac system, due to increased central venous pressure, and on the respiratory system, by decreasing total lung volume, pulmonary compliance, and functional residual capacity by 20%, which may lead to hypoxia, hypercapnoea and atelectasis [48], [49]. An increase in cerebral blood flow pressure could also impair cerebral circulation [48]. More marked changes may be observed in obese, elderly, or debilitated patients.

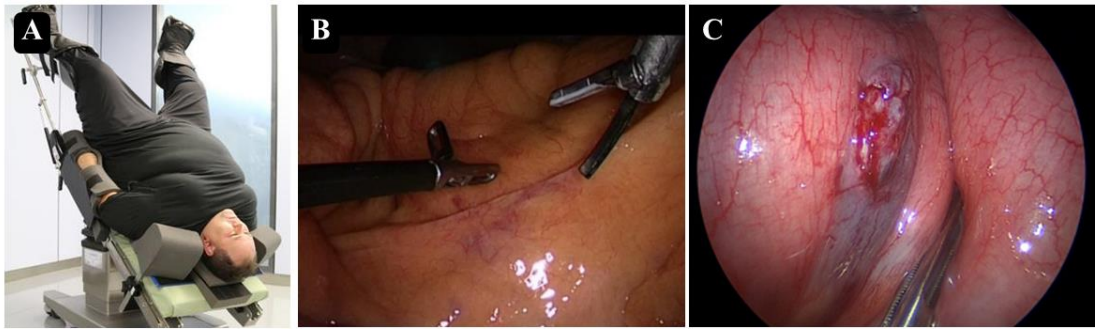


Figure 3.1 Current method to retract the bowel during laparoscopy with; A) the Trendelenburg position [50]**, B) bowel graspers being used to manipulate the tissue, and C) an example of trauma caused by bowel graspers** [51]**.**

In addition to TP, instruments are required to manipulate the bowel from the operating field of view. Commercially available devices are typically too small, difficult to operate, provide unsafe retrieval, and lack adjustability [52]. Non-crushing bowel graspers are the most common instrument used to manipulate and retain the internal organs (Figure 3.1 B). The surgeon relies on the haptic feedback from the graspers to delicately manipulate the internal organs. However, this feedback is severely limited due to the mechanical friction losses and variations in the transmission of forces over the working range [53],

[54]. Furthermore, the relatively small tips on the laparoscopic graspers can generate high pressures locally on the soft tissue (up to 200 kPa) [55], [56], which may lead to injury or perforation (see Figure 3.1 C). Conversely insufficient force will lead to tissue slipping out of the graspers. The intraoperative complication rate for laparoscopic colorectal surgery is between 7-9% with a rate of conversion to open surgery of between 9-13%. The rate of postoperative complications can be as high as 30% [57] with an incidence of postoperative ileus of between 15-20% leading to prolonged hospital stay [51]. One of the main causes of postoperative ileus is excessive force applied to tissues from conventional graspers.

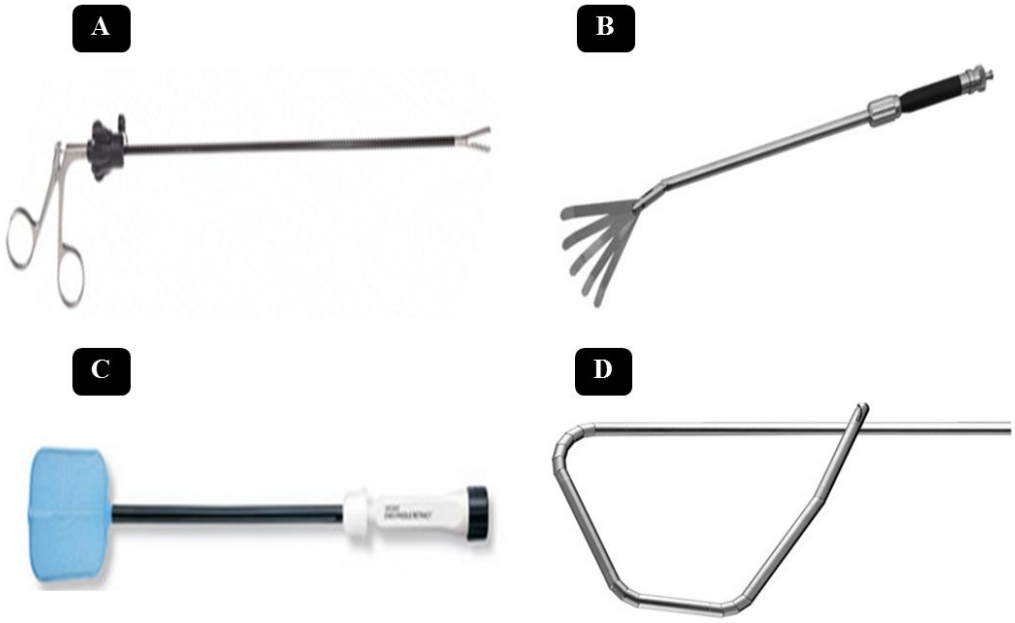


Figure 3.2 Commercially available bowel retractors: A) laparoscopic bowel graspers (Medline Industries, Inc., Mundelein, Illinois), B) laparoscopic Fan retractor (LocaMed Ltd., Farnham, Surrey, U.K.), C) the inflatable Endo Paddle™ retractor (Medtronic, Dublin, Ireland), and D) Snowden-Pencer triangular liver retractor (Cardinal Health, Dublin, Ohio).

An alternative to the bowel grasper which may be classified as an instrumental retraction technique, is the barrier retraction method [52]. Barrier retractors are inserted into the body in a collapsed state, deployed within the body and either held by an assistant or may be fixed to the operating table. Numerous disposable and reusable retractors are available. The fan retractor, which was originally designed for use in upper gastrointestinal surgery, works by rotating a dial in the proximal end of the device which in turn deploys a number of blades in a fan-like pattern once placed intra-peritoneally (Figure 3.2 B). The fan retractor must be observed closely when being closed as inadvertent organ injury may occur if trapped between the retracting

blades. In addition, the fan retractor is made from many small components, and runs the risk of spoiling the operating field if breakage occurs [52]. The Endo paddle retractor™ (Medtronic Covidien, Dublin, Ireland), which is a type of paddle retractor, operates in a similar manner. The Endo paddle retractor (Figure 3.2 C) comprises an inflatable paddle located on the distal end of a manually operated rod. After insertion, a balloon on the distal end of the rod is inflated providing a relatively wide palmated anterior surface which creates a soft interface between the balloon and internal organs. However, the small bowel may slip around the edge of the inflated surface and migrate into the operating field. The triangular retractor (Figure 3.2 D), which is a type of snake retractor, is primarily used in liver retraction. The retractor comprises hinged links along its shaft that can be manipulated into a curved profile by rotating a hand piece on the proximal end of the device. The triangular retractor can fit through a 5 mm operating port. However, the possibility of pinching the soft tissue between its links when engaged makes the device unsuitable for bowel retraction. In addition, the contact area between the shaft and the organ is quite narrow.

Despite their presentation as laparoscopic bowel retractors, the aforementioned devices do not present the critical characteristics to ensure their adoption as the standard of care in minimally invasive retraction [52]. The ideal retractor therefore has yet to be developed.

3.1.3. Laparoscopic Colectomy

Colectomy is a surgical procedure to remove all or part of the colon, and in extreme cases, the entire large intestine along with the rectum is removed (proctocolectomy). The laparoscopic approach towards colectomy is growing in both popularity and scope of indications. During laparoscopic colectomy, the bowel falls into the pelvis and must first be retracted in order to mobilise the blood flow to the colon before resection. As discussed in Section 3.1.2, this is most commonly achieved through the Trendelenburg positioning and utilising existing retraction techniques which are not ideal.

The most common application of colectomy is to resect malignant tumours (colon cancer) arising in the wall of the large intestine or rectum, in most cases from dysplastic adenomatous polyps [58]. Colon cancer is the second leading cause of cancer deaths among men and women in the US combined. Five percent of the normal population will be diagnosed with colorectal cancer in their lifetime. In 2014, 71,830 men and 65,000

women were diagnosed with colorectal cancer in the US [59]. Globally nearly 1.4 million new cases are diagnosed each year [60]. With 1.4 billion people currently overweight, incidence of colon cancer is predicted to significantly increase [61]. However, when detected early, it can be a treatable malignancy [62].

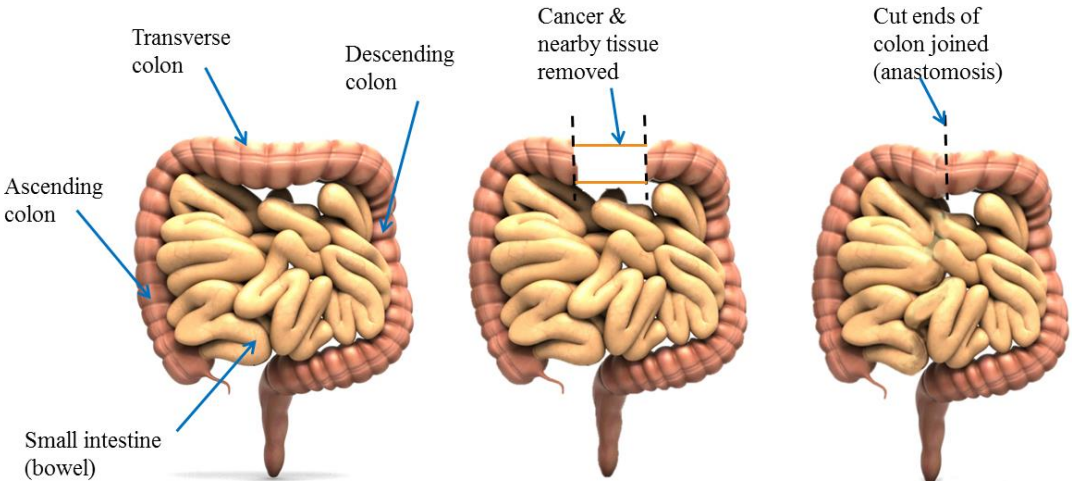


Figure 3.3 Colorectal surgery showing an example of anastomosis on a cancerous portion of the transverse colon.

Colorectal surgery is also performed to repair damage to the colon, rectum, and anus, caused by diseases of the lower digestive tract such as diverticulitis and inflammatory bowel disease (ulcerative colitis and Crohn's disease). Injury, obstruction, scar tissue and ischemia (compromised blood supply) may also require bowel surgery. Crohn's disease and ulcerative colitis, both chronic inflammatory diseases of the colon, affect approximately 1,000,000 young adults in the US. Surgery is recommended when medication fails patients with ulcerative colitis. Usually, surgery is drastic, removing the colon and rectum and creating an interior or exterior pouch to collect body wastes. Nearly 3/4 of all Crohn's patients face surgery to remove a diseased section of the intestine or rectum. Diverticulosis, the growth of pouches in the walls of the intestine, occurs in nearly 1/2 of all Americans by the time they reach age 60 and in practically everyone over 80. Diverticulitis may also require surgery to remove part of the colon if there have been recurrent episodes with complications or perforations [63].

3.1.4. Laparoscopic Hysterectomy

Laparoscopic hysterectomy is the surgical removal of the uterus, disconnecting it from its attachments, using long thin instruments administered through laparoscopic ports (see Figure 3.4). Like laparoscopic colectomy, the first step in removing the uterus located in the pelvis, is to retract the distended loops of the bowel from the operating field of view. In 70% of cases the surgical site is either partially or completely obstructed by the small bowel, making the procedure not feasible without retraction [59].

Figure 3.4 Laparoscopic hysterectomy instrument positioning [173]**.**

Hysterectomy is the second most commonly performed surgical procedures undergone by women in the US with 570,000 cases performed in 2006 [64], and accounts for $5 billion annually in US health care spending [65]. More than 80% are for treatment of benign diseases, such as leiomyoma, abnormal uterine bleeding, pelvic organ prolapse, and endometriosis. Endometrial cancer is the fourth most common cancer in women [59]. Approximately 40% of endometrial cancer patients need to have a para-aortic lymphadenectomy, which involves surgery in the area of the aorta, and vena cava. Minimally-invasive laparoscopic surgery has been demonstrated to be an effective tool for this procedure. Its use has been associated with decreased postoperative morbidity, pain, recovery time, operative time, and complications as well as increased patient satisfaction and quality of life [66].

For both laparoscopic colectomy and laparoscopic hysterectomy, which are two examples of lower abdominal procedures which require extensive bowel retraction, an effective solution which gently and effectively removes the bowel from the operating field whilst reducing the angle of table tilt, has yet to be developed.

3.1.5. Problem Statement

Based on end-user feedback and the current state of laparoscopic retraction, the following problem statement was defined:

To reduce intraoperative trauma and improve surgical access during lower abdominal laparoscopic surgery, in particular laparoscopic colorectal surgery and laparoscopic hysterectomy, by effectively and sustainably retracting the distended loops of the small bowel from the operating field of view.

A list of design requirements was derived from end-user surveys, literature review [52] and competing technology assessment. The essential design requirements include:

1. Outer diameter less than 5 mm to accommodate minimally-invasive insertion,
2. The device should be light weight, easily deployed and easy to use,
3. Provides a sustained and reliable field of view through retraction of the bowel,
4. The device must be atraumatic and resist leakage,
5. It must be ergonomically designed to optimise its operation over a prolonged time,
6. The ability to be used in a confined space without obstructing the surgical view,
7. Capable of removal and further reinsertion without incurring damage before disposal.

3.2. Prior Work

The design history of the SecuRetract project has changed significantly since the original concept was proposed as part of the UCC BioDesign module. This section will summarise the prior work carried out on the SecuRetract project as part of the author's MEngSc thesis (see Figure 3.5), before moving onto the additional improvements as part of this research [8].

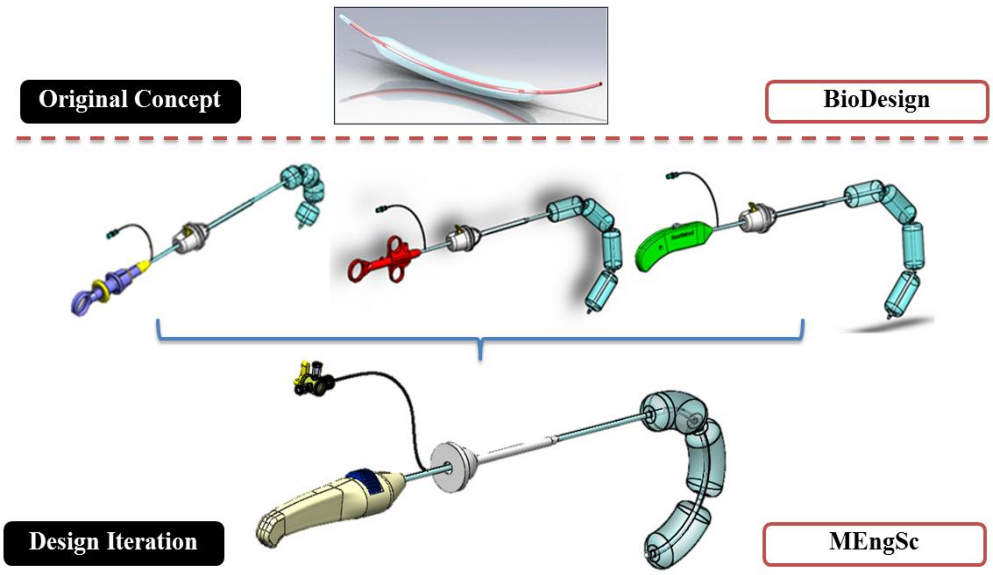


Figure 3.5 Design evolution overview from original concept through succeeding iterations as part of a research Masters.

3.2.1. Summary of MEngSc Development

The retractor project became the subject of a Masters by research project supported by an Enterprise Ireland Commercialisation award which the author concluded in July 2013. The MEngSc research and design concentrated on a stand-alone device with a control handle and curvable distal end capable of engaging and manipulating the distended loops of bowel and its connecting mesentery (a fold of the peritoneum which attaches the small intestine to the posterior wall) [5], [7], [8].

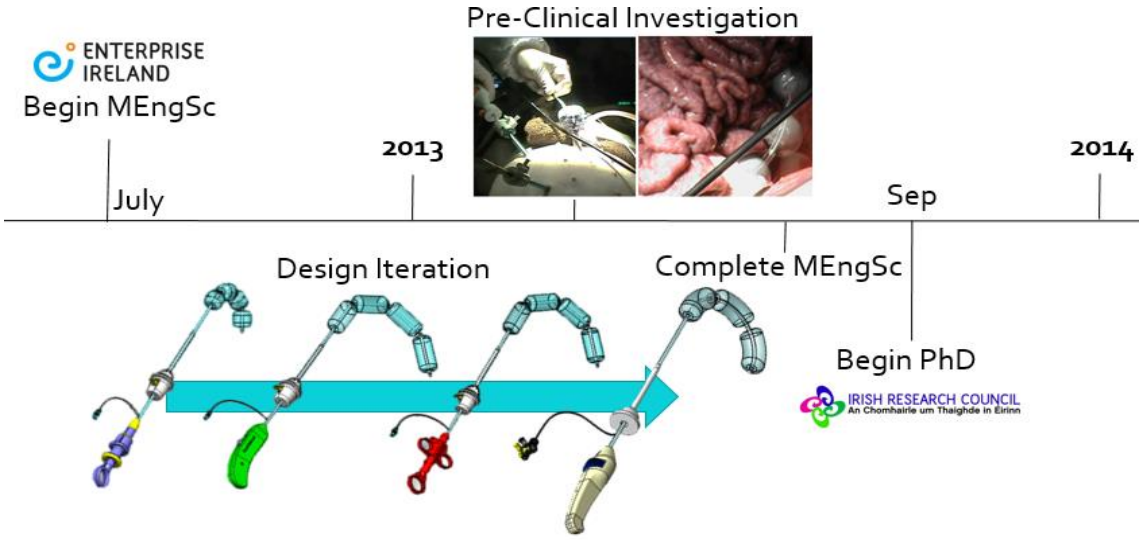


Figure 3.6 Sequencing of prior work timelines.

After an iterative design process, the final laparoscopic retractor designed as part of the MEngSc thesis, comprised a control handle, a central shaft, and a number of inflatable balloons mounted to the distal end of the device (see Figure 3.7). The design was produced using SolidWorks® (Dassault Systèmes SolidWorks Corp., Waltham Massachusetts) before developing prototypes in-house using a Dimension Elite 3D Printer (Stratasys Ltd., Minnesota, USA), and a HURCO CNC machine (Hurco Companies, Inc., Indianapolis).

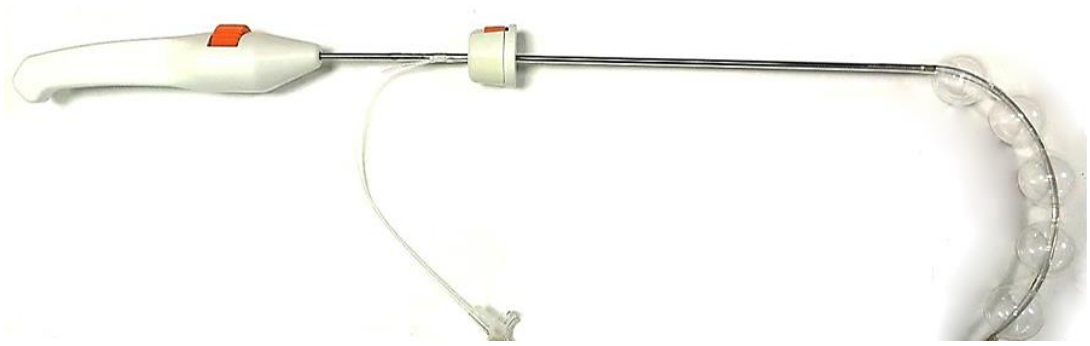


Figure 3.7 Retractor prototype pictured in its inflated, curved position with non-return inflation valve.

The distal end of the device comprised five modular dilation balloons mounted in series to co-axially extruded tubing which sheaths over the leaf spring and central shaft providing an air tight encasing. The co-axial configuration facilitates inflation of the dilation balloons and the modular balloons provide a large cushioned surface on retraction (see Figure 3.8 B). The balloons and tubing fabrication was supplied by Creagh Medical Ltd., Co. Galway, Ireland.

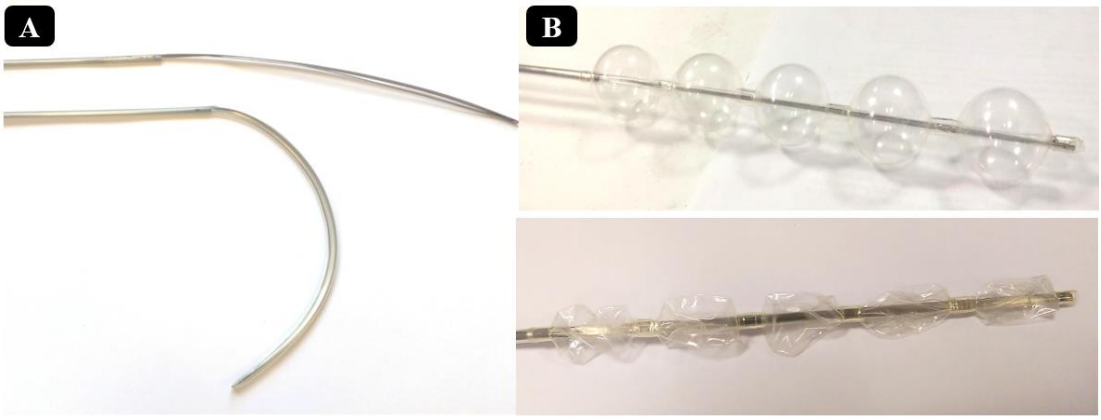


Figure 3.8 A) Spring beam design pictured in the straight and curved positions, and B) modular balloon design pictured in the straight inflated and deflated positions [5], [7], [8]**.**

The material used to create the printed handle prototypes was acrylonitrile butadiene styrene (ABS). ABS is a common thermoplastic used in rapid prototyping with a glass transition temperature of approximately 105°C. The handle design comprised a thumb dial with an axis of rotation parallel to the shaft. As the dial is rotated it axially displaces a lead screw fixed in rotation which further displaces a wire that terminates at the distal end of the leaf spring. The degree of curvature of the distal end may be controlled by the thumb dial up to a fully curved position, creating a radius of curvature of approximately 60 mm.

3.2.2. MEngSc Prototype Evaluation

The displacement of the spring beam was simulated using the finite element analysis (FEA) tool, Strand7 (Strand7 Pty Ltd., Sydney, Australia) to characterise its performance. The simulated FEA model used geometrical and material inputs matching the properties of the spring beam [5]. The analysis determined that the beam would experience a maximum stress of 450 MPa on deflection, which is 1.3 times less than the yield strength of the carbon steel (586 MPa). The analysis also predicted a linear relationship between the axial force applied to the modelled internal wire and the corresponding deflected angle (see Figure 3.9)

Physical bench-top experimentation subsequently corroborated the simulated results (Figure 3.9 B). It was determined that an axial tensile force of approximately 20 N is required to deflect the beam about an angle of 80 ± 3° from the normal position. The restoring force required to return the beam to the straight position measured in excess of 5 N which exceeds the maximum pull force required to stretch the mesocolon for dissection as reported by Visser *et al.* (2002) (average pull force to stretch the mesocolon 2.4 ± 1.1N, maximum force measured was 4.7 N) [67].

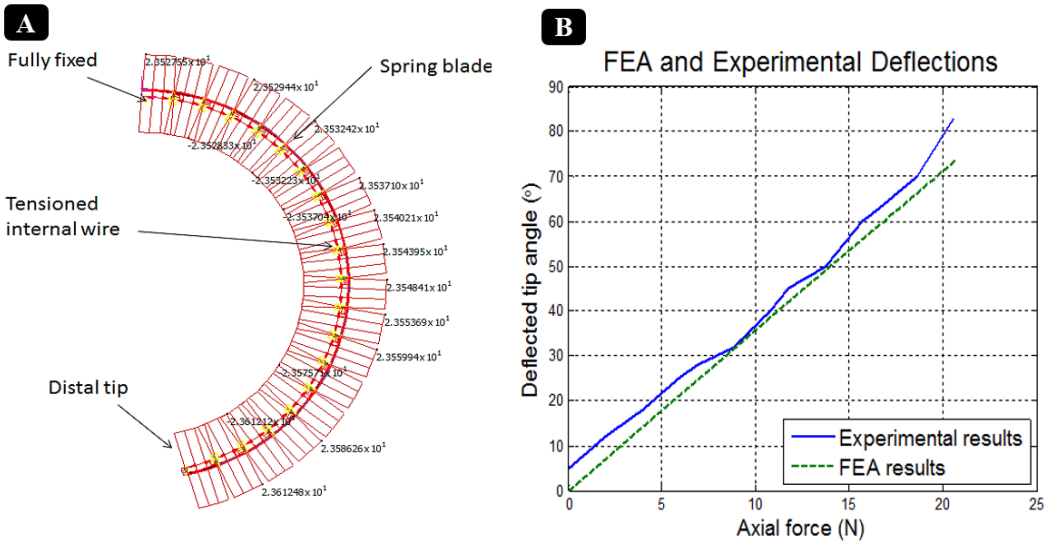


Figure 3.9 A) simulated FEA model of the axial tension experienced by the internal wire used to displace the leaf spring, and B) simulated and experimental axial tensile force comparison plot [5]**.**

The balloons were also evaluated using bench-top experimentation. The preferred inflation diameter of 30 mm occurs at an inflation pressure of approximately 260 mmHg with a combined surface area of approximately 250 cm^2. The burst pressure was rated at approximately 428 mmHg for an elongation at break of 800%. This results in a tensile strength of approximately 15.6 MPa [5], [8].

3.2.3. Pre-Clinical Investigation

The MEngSc prototype was laparoscopically deployed *in vivo* in a porcine model and its performance was recorded using laparoscopic video. The pre-clinical animal investigation endpoints were technical feasibility and safety. This investigation, which took place in May 2013, was approved by both the Irish Department of Health and UCC animal experimentations ethics committee. The porcine model is a close anatomical model for the human digestive system, and is an ideal model for the technical evaluation of new medical devices in colorectal applications.

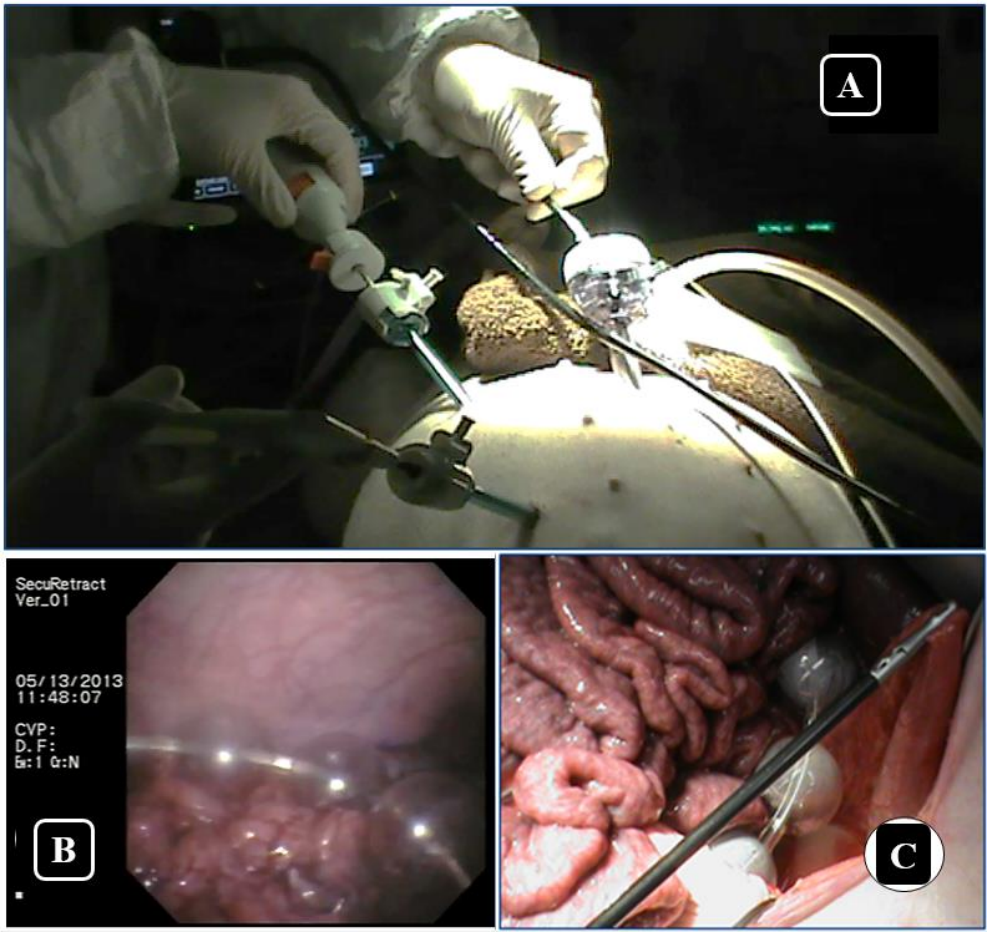


Figure 3.10 Prototype used in a pre-clinical animal investigation. (A) External view of the device passing through laparoscopic port. (B) View from laparoscopic camera of the distal end of the retractor engaging the bowels. (C) View of the retractor's placement around the bowels during a conversion to open surgery to better visualise the operation of the retractor.

The model used was a female Landrace pig weighing 26.7kg. The animal was sedated for the duration of the procedure and was euthanized immediately following the procedure without any recovery. Three laparoscopic ports were inserted through the abdominal wall (2 x 5 mm and 1 x 12 mm trocars), the largest of which accommodated a laparoscopic camera (Olympus Evis Exera BF type 160 series) (Figure 3.10 A). The peritoneum was inflated to 15 mmHg CO_2 with an Olympus UHI-3 insufflator (Olympus, Pennsylvania).

The pre-clinical investigation was carried out by a consultant colorectal surgeon with over twenty years of surgical experience. The retractor was inserted into the upper right quadrant through a 5 mm trocar in its deflated and straight form. Once positioned within the peritoneal cavity, the retractor was engaged to hook around the bowel and its associated mesentery. The mesentery holds the bowel to the posterior wall, thus provides an anchoring point to retract the bowel. The device was then

inflated, creating a large, soft interface before withdrawing the distended loops of the small intestine from the pelvis to a position higher up in the abdominal cavity (see Figure 3.10 B). The prototype was then deflated and removed back through the surgical port only to be repeatedly reinserted and evaluated in both the left upper quadrant and right upper quadrant. Further tests evaluated the effectiveness of mesentery manipulation for inferior mesenteric arch and lymph node access. The investigation concluded with an open surgical investigation to allow clear visualisation of the retraction process (Figure 3.10 C).

3.2.4. MEngSc Design Discussion

Simulated and physical modelling was used to evaluate the MEngSc device design. The physical model closely resembled the simulated calculations reflecting the elastic nature of the spring steel and the tensile force applied to the internal wire. In addition, the engaged device commands sufficient rigidity to retract the bowel from the operating space (> 5N).

The pre-clinical animal investigation proved successful in assessing technical feasibility of the retractor. The light weight retractor (0.085 kg) was repeatedly inserted through a 5 mm diameter trocar. During the study, the prototype was inflated and deflated, and repositioned several times without damaging the internal tissue. Initially the animal was temporarily placed in the Trendelenburg position, and the prototype was positioned to hook around and engage the mesenteric bowel. Once in place, the animal was returned to the supine position and the retractor successfully maintained the bowel from operating field of view.

However, the pre-clinical investigation did have its limitations. Due to the subjective nature of this study, it was difficult to obtain quantitative data. The porcine gastrointestinal tract, albeit similar in anatomical make-up, was different in size and weight compared to a human's. Therefore, the pre-clinical study was primarily a technical feasibility study of the device. The pre-clinical trial and physical evaluations identified a number of necessary design improvements which include device orientation, labelling and ergonomic modifications to the handle design which are presented in later sections.

3.3. PhD Design Development and Evaluation

The bowel retraction project was continued as part of this PhD thesis which aimed to overcome the limitations of previous design and to develop a design for manufacture. The continued PhD research also aimed to carry out a more expansive review of the commercial potential of the proposed device as well as engaging with key-opinion leaders and identifying clinical champions for early device adoption.

3.3.1. PhD Design Development

As a result of the previously described evaluation methods, a number of design modifications were made to the retractor design as part of this work. The prototype used in the pre-clinical investigation curved about a plane parallel to the frontal view of the device (i.e., up-down). However, clinical feedback noted that it would be more intuitive if the device curved from left to right as the thumb dial was turned clockwise (i.e. a plane parallel to the top view of the device). It was independently noted that over time, the carbon steel leaf spring began to show signs of corrosion. Therefore stainless steel (grade 301) was sourced and the beam profile was cut from the sheet using a laser cutting process.

During the pre-clinical investigation, one of the dilation balloons were damaged most likely due to inadvertent contact with the bowel graspers. Therefore a more robust balloon design was sought. A number of balloon and tubing configurations were explored ranging from the original spherical dilation balloons to cylindrical elastomeric balloons (see Figure 3.11 A-C). Highly-compliant polyurethane balloons were chosen as they present a number of performance related advantages. In the first instance, elastomeric balloons shrink to a much tighter profile in comparison with dilation balloons. The highly compliant nature of the balloons and tubing closely conforms to the curvature of the central shaft when actuated and the elastomeric material ensures elastic behaviour during the inflation and deflation cycles which allow the balloons to deflate completely and rapidly (approximately one second). The compliant balloons (fabricated to design specification by Creagh Medical, Co. Galway, Ireland) were mounted to a co-axial tubing as before. The embodiments of one single long balloon and three cylindrical balloons were investigated (see Figure 3.11 B, C). However, it was found that the best working design was with three modular cylindrical balloons. This modular alignment follows the curvature of the

shaft more closely and is quicker to inflate and deflate compared to the single long balloon configuration. The single long spherical balloon does not follow the internal curved shape as closely as there are no restriction points along its length. In addition, three balloons require less bonding points compared to the five spherical balloon design and presents fewer gaps along the curved area.

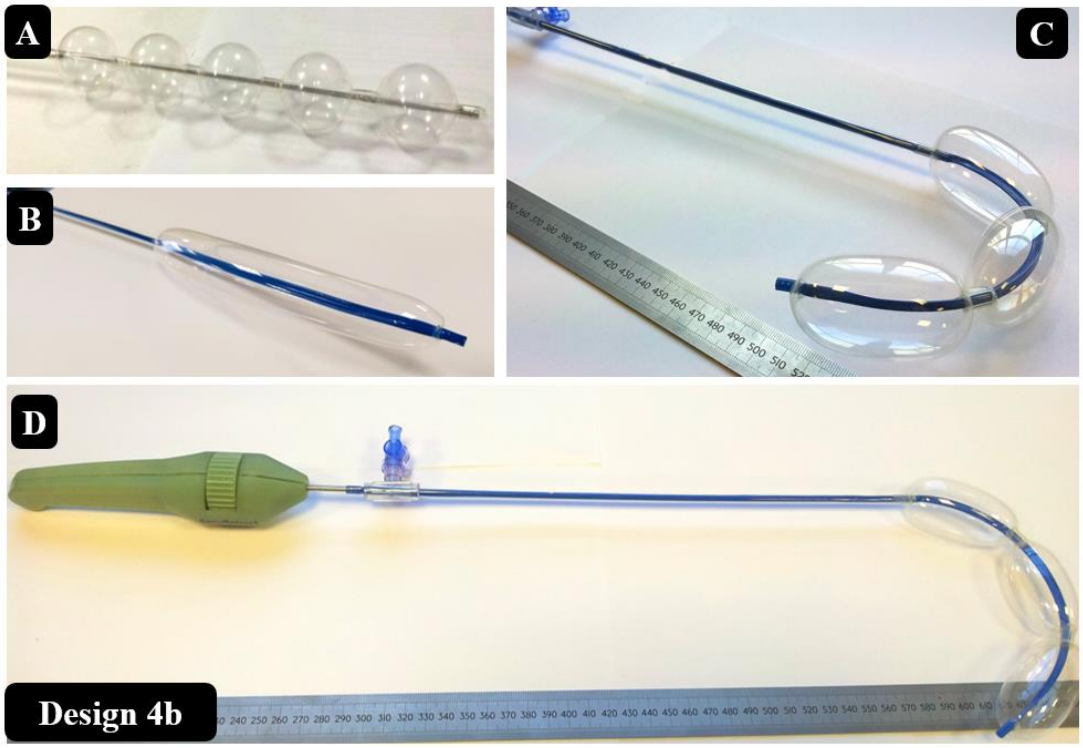


Figure 3.11 Compliant tubing and balloon configurations with (A) five spherical dilation balloons as developed during the MEngSc thesis, (B) one single long cylindrical elastomeric balloon, and (C) three shorter cylindrical elastomeric balloons, and the assembled device with updated handle design (D).

The fully actuated position of the handle design is predetermined by an inbuilt stop which prevents excessive curvature at the distal end. However, as observed during the pre-clinical investigation, the user may overexert the force on the dial forcing the internal displacement bolt against the internal stop. This may cause handle deformation and or force the two sides of the handle apart. The handle was therefore analysed to determine the magnitude of deformation. SolidWorks® simulation tool was employed which assumes static loading and linear elastic behaviour. The material assigned to the handle was ABSplus-P430 (elastic modulus (E) of 2.2 GPa, yield stress (σ_{yield}) of 33 MPa [68]) to correspond to the 3D printed prototypes. The results highlighted peak stress areas within the model which subsequently led to modifying the geometry and increasing wall thickness at specific locations until an acceptable deformation was obtained. Simulated

external force of 20 N (10 N per side) was applied for FEA analysis. This represents the maximum translational force that the user may distribute from the dial to the axially acting displacement bolt determined from physical testing. The simulated results identified a peak stress value of 3.98 MPa which is significantly less than the yield stress (factor of safety of 8.3), and a maximum resultant displacement of less than 0.04mm (see Figure 3.12).

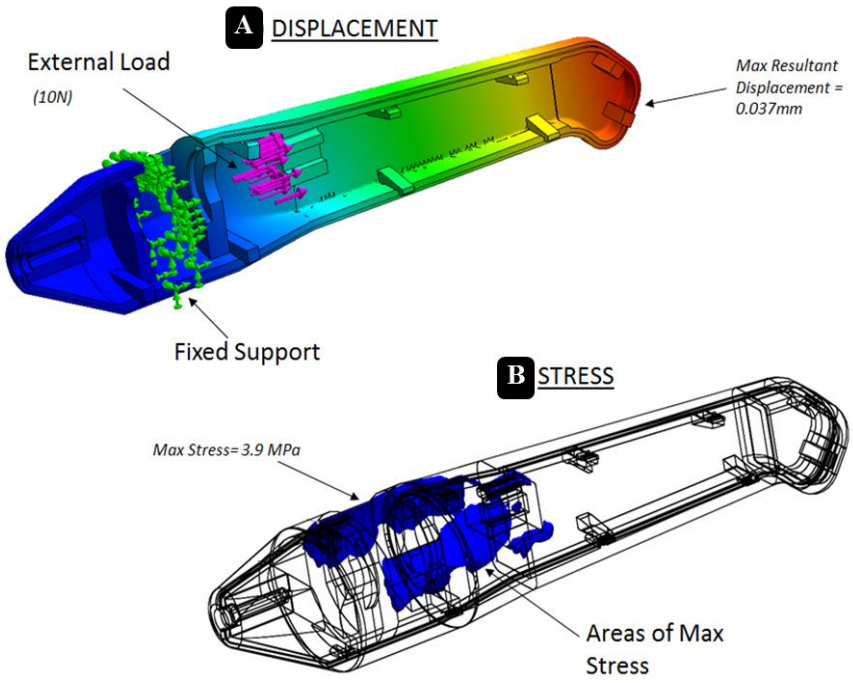


Figure 3.12 FEA analysis of the handle illustrating (A) the maximum resultant displacement and (B) the areas of maximum stress for an external applied load of 10N per handle part [5]**.**

The updated design (see Figure 3.11 D), which comprised a re-oriented shaft and re-enforced snap-fit handle design, was presented to a number of end-users (n=10) for appraisal of clinical utility. Despite presenting an ergonomic and functional solution, the thumb dial handle offers a brand new feel and design compared to currently available instruments which may lead to reluctance in clinical adoption. Clinicians from the Cleveland Clinic Ohio, Cork University Hospital, Mercy University Hospital, and the Mater Misericordiae University Hospital, all welcomed the atraumatic hooking action of the retractor as a novel and attractive solution to increasing surgical access during keyhole surgery. However, it was noted that a scissor-like handle design would be more in-line with currently available laparoscopic instruments. A scissor-like design presents a level of familiarity and confidence of use similar to the conventional handle on a bowel graspers pictured in Figure 3.2 [7].

3.3.2. Continued Design and Development

As a result of listening to the "voice of the customer", the author revisited the control handle design of the laparoscopic retractor. A clear desire amongst the medical community is to balance familiarity of use with operational benefit. Initially a very simple, two part design was developed with ratcheting interlocking segments (see Figure 3.13). However, this design does not present the ergonomic and functional performance desired. Subsequent to rapid prototyping this solution and presenting the solution to the clinical advisors (Dr Andrews and Dr O'Riordain), it was noted that feel of the device was not ideal. The perpendicular position of the finger grips relative to the shaft results in additional stress on the wrist to orient the distal end correctly. Despite this finding, the physicians recognised the advantage of moving towards a scissors design, albeit with further design being required.

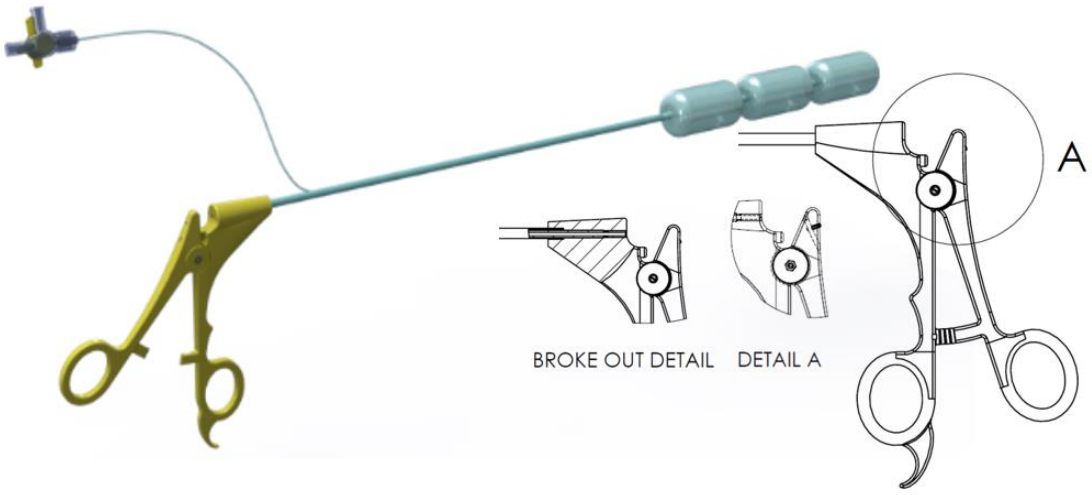


Figure 3.13 Scissors handle design concept generated using SolidWorks® computer design software.

The scissors handle concept was subsequently developed further in collaboration with Dolmen industrial design house (Dolmen, Dublin 1). Dolmen's expertise lies in product design with a specific focus on human factors design. Subsequent to a national tender process, Dolmen were contracted to work with the author to develop an ergonomic handle design suitable for manufacturability, supported by the Enterprise Ireland Commercialisation award. Initial rough sketches were developed based on visual research of commercially available technologies (see Figure 3.14).

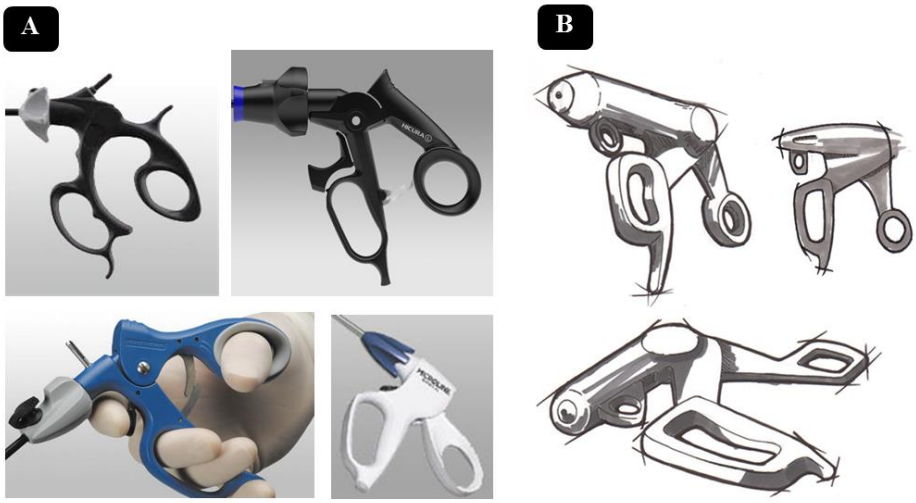


Figure 3.14 A) Visual research of commercially available surgical handles and B) early stage sketch development by Dolmen industrial design house, Dublin.

Once the general form-factor was agreed, a number of iterative designs were developed using SolidWorks® (see Figure 3.15). Each iterative design was printed in-house with ABS before being assessed by the project team.

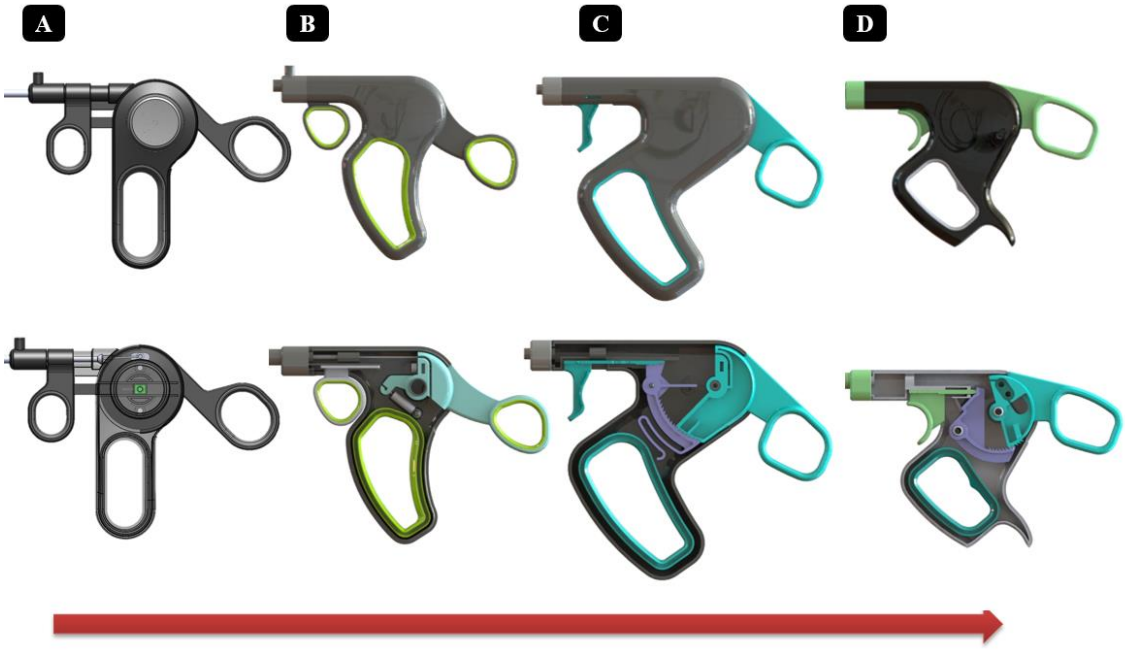


Figure 3.15 Control handle Design 5 iteration (A-D) with both covered and exposed internal design.

As part of the works with Dolmen, the author and the Dolmen design team maintained weekly updates. As the design was iterated, in-house facilities in UCC were leveraged to 3D print and evaluate each iteration for ergonomics and functionality. Table 3.1 summarises the key design change decisions between the iterations in Figure 3.15.

Table 3.1 Revision history of UCC-Dolmen SecuRetract handle iteration.

Rev	Description of Current Design	Reason for Design Change
A-B	Roller clutch bearing with instantaneous back stop to lock handle in place. Bearing unit cost €2/quantity of 500. Trigger used to release bearing to allow retractor to return to straight position. 8 moulded parts in total.	Replace bearing with spring to reduce unit costs. Reduce number of moulded parts to 6. Introduce curve for finger slots to improve ergonomics.
B-C	Trigger release and thumb lever solution with curved finger slots to accommodate the second, third and fourth fingers. Enclosed index finger grip on trigger.	Space between the handle housing needs to be made larger to accommodate locking mechanism. The alignment between the index finger and second to fourth fingers should be improved for ergonomics. Enclosed release trigger may present a risk of accidently trapping the index finger resulting in accidental discharge.
C-D	Larger handle design to accommodate internal locking mechanism which further comprises a compliant toothed locking design released by a trigger. Positions for all fingers have been adjusted. Open trigger design.	Compliant internal locking component fractured during prototype evaluation. Overall size of handle is too large (distance from trigger to centre of thumb lever is 11.5cm).
D	Overall size reduced (index to thumb = 9cm) and compliant locking mechanism replaced with torsion springs. Left and right housing mate with multiple snap fit connections.	

As summarised in Table 3.1, the internal ratchet arm of design C was prone to failure (see **Error! Reference source not found.**). Figure 3.16 illustrates the failure experienced at a corresponding point of maximum stress as determined through FEA simulation with SolidWorks® static simulation tool. Despite a maximum stress of 34 MPa, which is approximately half the flexural yield strength of ABS (60-73 MPa), fatigue analysis determined that after eleven cycles, the part would have a 100% chance of failure at the point of maximum stress.

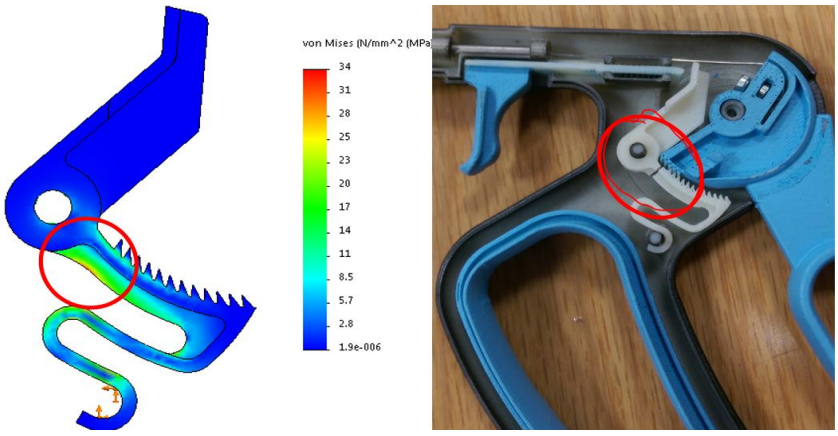


Figure 3.16 Compliant ratchet failure in Design C.

Subsequent to the failure analysis and a recognition that design C presented a solution which was too large for the average human index to thumb span, the team arrived at design D (see Figure 3.18). The compliant locking mechanism was replaced by a torsion spring. The specification of the torsion spring was dependent on the available geometry. The designated spring comprised of the following specifications:

- Wire diameter: 0.8mm
- Outer diameter of Spring: 12mm
- Inner diameter of spring: 10.4mm
- Number of active coils: 2.625
- Body length: 2.9mm
- Leg length (both leg 1 and 2): 15mm
- Direction of wind: left hand

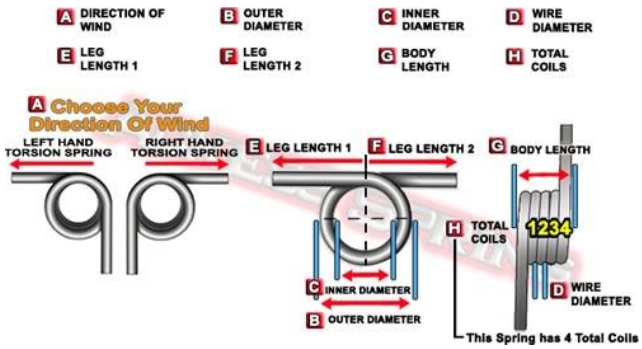


Figure 3.17 How to measure torsion springs from www.acxesspring.com.

For material such as music wire (ASTM A228), the torque rate per degree for the above specifications is 0.741 N-mm/degree and max torque of 80.228 N-mm (max safe travel 108.2 degrees) which provides 3.6 times the required travel (lever rotation: 30°).

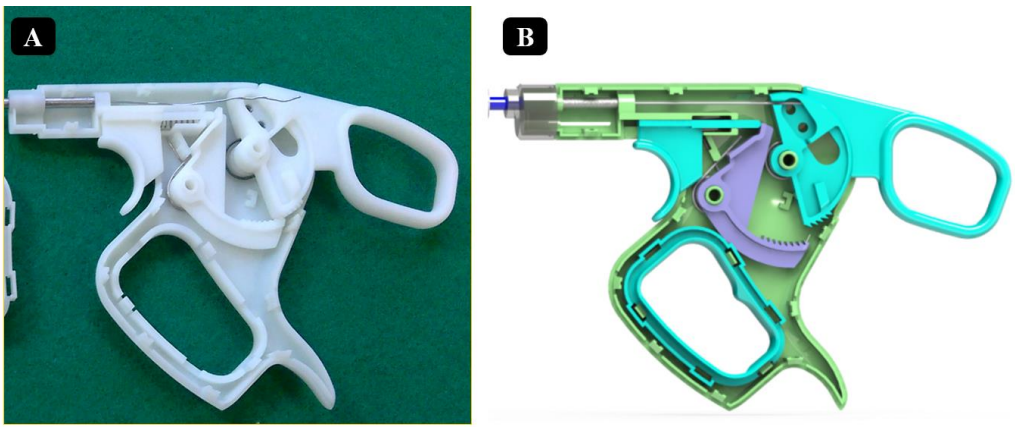


Figure 3.18 A) handle Design D printed prototype, and B) corresponding computer drawing.

3.3.3. Prototype Evaluation

The updated balloon design described in Section 3.3.1 along with the final collaborative effort between the author and Dolmen was assembled and presented to a cohort of approximately twenty physicians (see Figure 3.19).

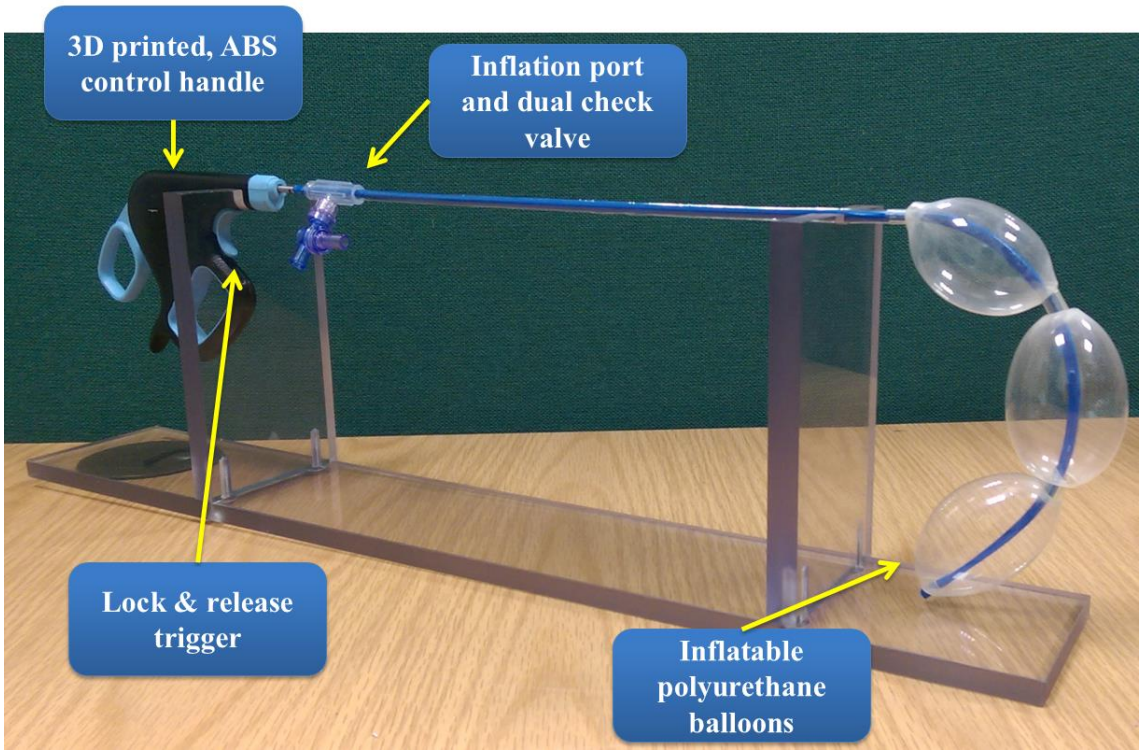


Figure 3.19 Final SecuRetract design, Design 5, pictured in the inflated and curved position with key features highlighted.

The assembled device was assessed in a simulated abdominal model for usability (see Figure 3.20). The model provides a demonstration platform to carry out bench top experimentation of device insertion and removal through a five millimetre port, review of the inflation and deflation protocol and an understanding of the usability of the device. Ultimately this model may be used to engage with physicians to trial the device in a simulated environment. The model, which includes three instrument ports, represents the technical challenges of clashing instruments in the confinements of the abdominal cavity. The model also allows for comparison to commercially available retraction instruments (e.g. with the single use Endo Grasp™ 5mm grasper (Medtronic, Dublin)). The simulated model comprises a semi-cylindrical Perspex dome to represent the anterior abdomen with an internal diameter of 305 mm (circumference approximately 950 mm), which is comparable to the mean adult female waist aged twenty years and over (mean 952 mm) [69].

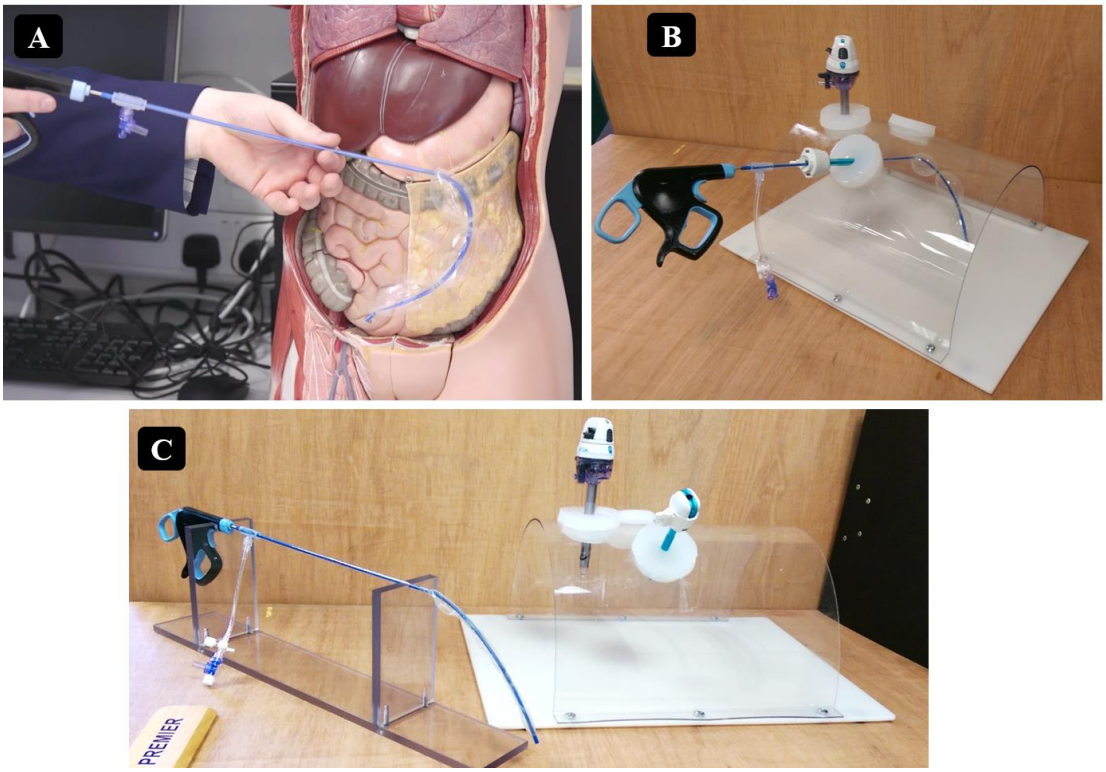


Figure 3.20 SecuRetract picture with anatomical model of the bowel (A) as well as pictured inside a simulated abdominal model (B, C) for usability assessment.

Three silicone rubber inserts were included in the model to facilitate instrument port placement and to imitate the rotational behaviour of trocar use through the soft abdominal tissues. The selected silicone rubber (Ecoflex® Series, Smooth-on, Macungie, PA) has a shore hardness of 00-30 (ASTM D-2240) and elongation at break of 900% [70]. The silicone inserts were characterized for penetration force with an 18 gauge Tuohy needle using a TA.HDPlus Texture Analyzer (Texture Technologies, Hamilton, MA) fitted with a 5 kg load cell. The system was controlled using a desktop computer running Texture Exponent v3.2 (see Figure 3.21). The maximum measured force through a 30 mm thick cylindrical sample was 6.4 N which is comparable to the maximum cutting force through the abdominal wall with a Veress needle (4.8 ± 0.8 N) [71]. The 30mm thickness is also representative of the average abdominal wall thickness in adults (23 ± 8 mm [72]). The performance of the silicone was noted by the clinical advisor to represent inpatient conditions closely, allowing for the port to pivot while protruding through soft material.

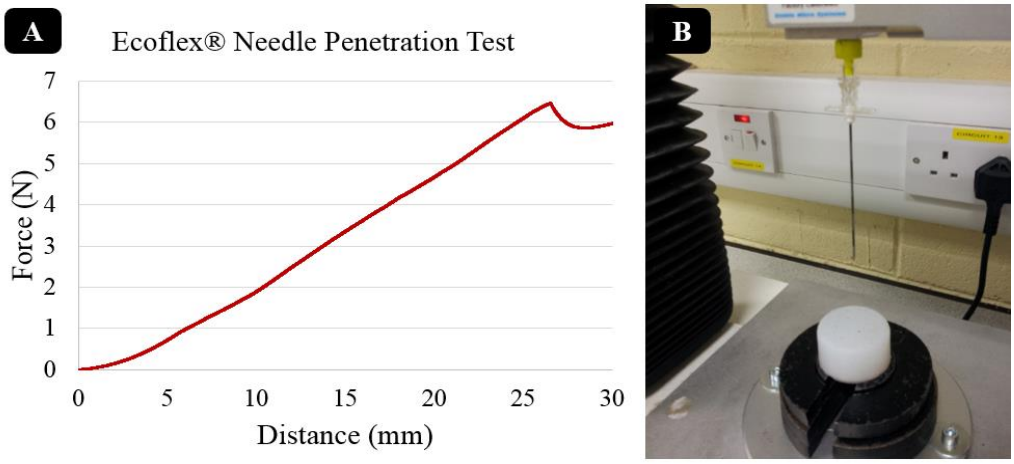


Figure 3.21 Ecoflex silicone rubber penetration test results (A) and experimental setup (B) using a texture analyser.

High resolution (50 μm) 3D printed handles were subsequently fabricated (Proto labs UK). During the assembly process, it was noted that the snap fit design tended to result in a failure of the male snap fit connections which tended to break apart (see Figure 3.22). FEA analysis identified that excessive buckling at the male extension of the snap fit connection exceeded the limits of the material (ABS) yield strength resulting in an immediate fracture of the male extrusion. Furthermore, a snap-fit design presents additional tooling considerations for injection moulding requiring additional tooling to accommodate the undercuts of the female end of the connection.

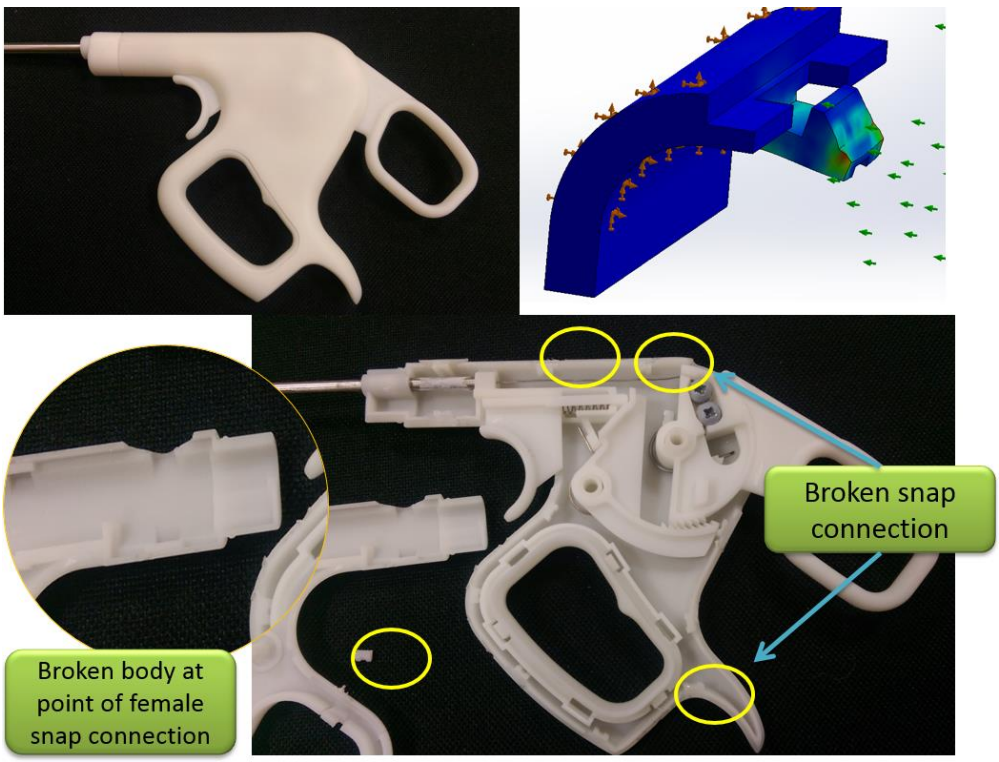


Figure 3.22 Fracture during assembly of snap fit connections.

3.3.4. Final Design

The snap fit connections discussed in Section 3.3.3 were subsequently replaced with a press fit design and the cap and finger insert were removed to further reduce the number of components in the handle to five. A draft of 3° was applied throughout the model to cater for tool parting on injection moulding. The internal mechanism and bending member configuration were unaltered from the previous design iteration.

The final SecuRetract design is deployed through a standard 5 mm diameter trocar in a straight and deflated position. Once positioned within the patient's abdominal cavity, SecuRetract is curved and inflated creating a unique bowel hook. SecuRetract provides a soft and effective means to gently pull impeding organs such as the bowel from the operating field (see Figure 3.23). The labelling requirements for medical devices and symbols to be used are outlined in ISO 15223-1:2016. An example of a possible label including symbols for single use, sterilisation method and references to lot numbers and shelf life is demonstrated below.

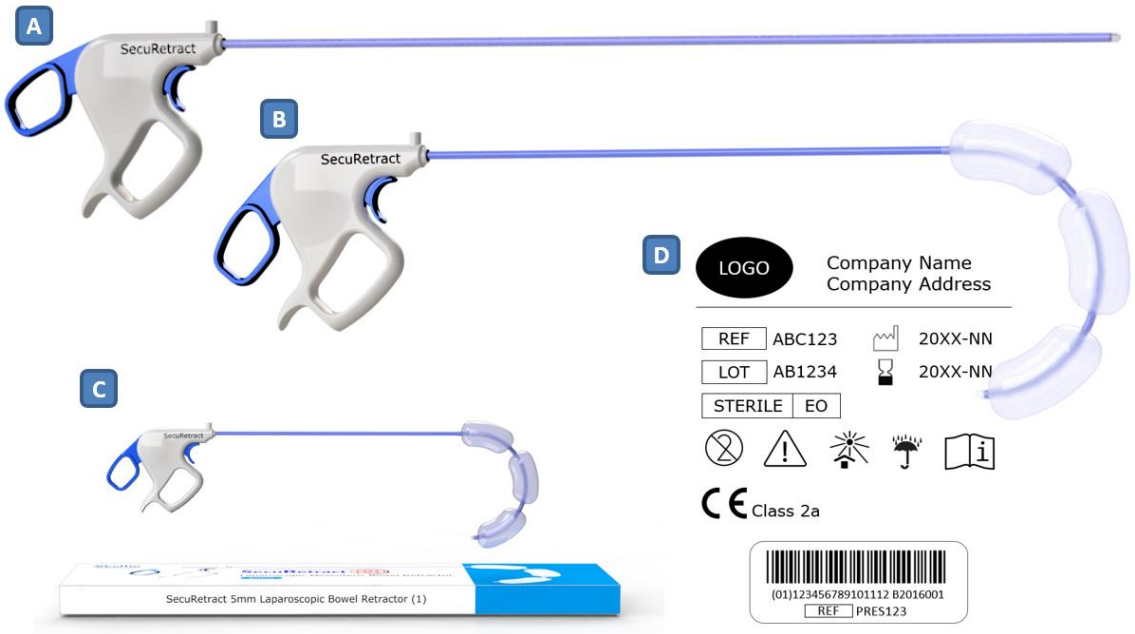


Figure 3.23 Final SecuRetract Design with A) & B) the device in the initial and deployed positions respectively, C) packaging render and D example of possible product labelling.

Final design transfer to manufacture, including documenting work instructions, production specifications, process failure mode and effect analysis and equipment qualification has yet to be finalised. These activities, as well as any further clinical evaluations will be conducted by the legal entity responsible for commercialisation.

3.4. Laparoscopic Retractor Commercial Feasibility

As part of first phases of the design control process, the student design team should examine the commercial feasibility of the proposed medical device. The commercial feasibility assessment accomplishes two things. First of all it explores whether there is a gap in the market and an appetite amongst the clinical community for the proposed invention to justify the project investment requirements. Secondly, reviewing the market and market requirements provides inputs into the design control process. In the context of the SecuRetract project, it is a further intention of the author to commercialise and market the laparoscopic retractor presented in this work through a university spin-out company. In 2015, the SecuRetract project was awarded its second Enterprise Ireland Commercialisation award with the aim of bringing the solution to a point ready for investment and market readiness. The following section briefly describes the market and commercial opportunity as well as providing feedback from key opinion leaders on SecuRetract's commercial potential.

3.4.1. Laparoscopic Device Market Opportunity and Trends

The global laparoscopic device market is valued at $9.5 billion, with a projected growth to over $14.8 billion by 2025 and a compound annual growth rate (CAGR) of 6.5% [73]. North America and Europe will continue to account for more than 60% of global laparoscopy devices market to 2019 [74]. Today there are approximately 10.7 million laparoscopic procedures performed worldwide [75]. Qualitative feedback from surgeons has suggested that SecuRetract has utility in 1/3 of these procedures [6] which translates to a total available market of over 3.5 million procedures.

As described in Sections 3.1.3 and 3.1.4, both colorectal and hysterectomy surgical procedures require extensive bowel manipulation to isolate the target organ for surgical intervention. Hysterectomies are generally described as a subset of the gynaecological market along with ovarian cyst removal and tubal ligation. The laparoscopic colorectal and gynaecological markets are forecasted to reach a collective value of $6.58 billion in 2025 with a CAGR of 7.1% and 6.1% respectively (see Figure 3.24).

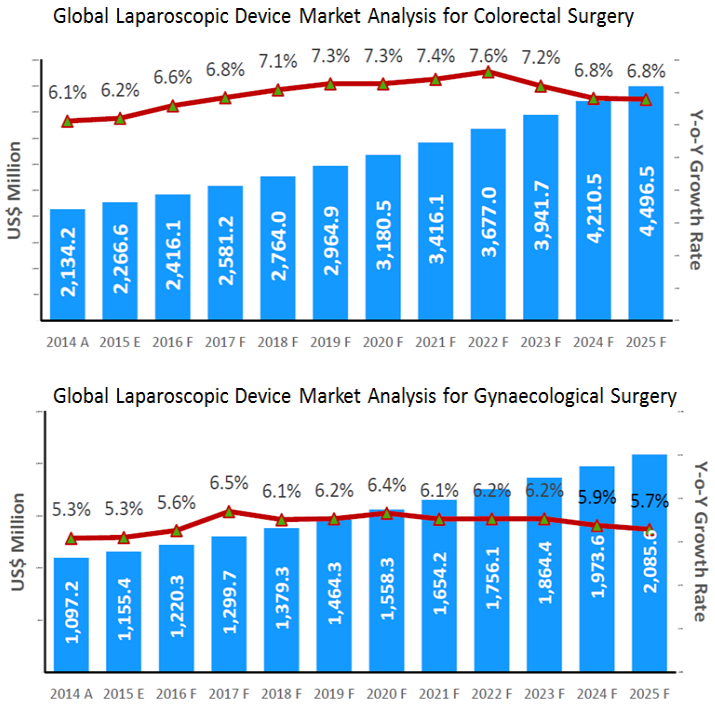


Figure 3.24 Global laparoscopic device market value share of colorectal surgery and gynaecological surgery [74]**.**

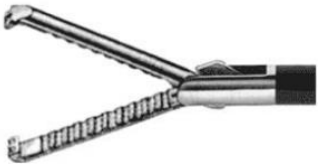
Colorectal surgery is expected to be the fastest growing application with an average CAGR of 7.1% with gynaecological surgery having a CARG of 6.1% [74]. Today the total number of colorectal and hysterectomy procedures carried out annually in the US and EU is estimated to be between 2 - 2.7 million procedures [59], [64], [74], [76], [77], of which approximately 0.8 – 1 million (40%) are performed laparoscopically as extrapolated from available market data [76], [78]–[80].

The rise in obesity in the U.S and Canada (34.9% of the 2014 adult population) will lead to increased risk of colon cancer [81]. In Western Europe, the laparoscopic devices market is expected to witness robust growth, mainly attributed to government policies such as diagnosis-related group (DRG) reimbursement, which provides opportunities to hospitals to upgrade their surgical devices and techniques for more economical and technically advanced procedures. Other drivers towards increased trends in laparoscopic surgery include rising private and foreign investments in the laparoscopic devices market, promotional activities in developing regions, and growing popularity of single incision laparoscopic surgery [74].

3.4.2. Current Technologies

The laparoscopic device market is a competitive landscape. Ethicon (Johnson & Johnson), Covidien (Medtronic), Karl Storz, Olympus, Cook Medical, and Richard Wolf all provide versions of laparoscopic instrumentation. However, to date an effective laparoscopic retractor capable of atraumatic retraction of the distended loops of bowel has not been developed [52]. As listed in Section 3.1.2, the most common instrument presently used to retract the bowel is the retraction graspers. In addition, a number of inflatable deployable retractors have been developed to overcome the trauma associated with the graspers. The following table illustrates the reported strengths and weaknesses of some select retraction instruments.

Table 3.2 List of deployable, atraumatic laparoscopic retractors and their associated strengths and weaknesses.

Competitor	Strengths	Weaknesses
Retraction Graspers 	Standard, low profile (5 mm diameter port). Several versions and manufacturers	Tissue trauma and injury, mechanical friction losses, high local tip pressure, tissue slippage at tip
EndoPaddle™ (Covidien) 	Large inflatable contact area, easily and quickly deployed	Requires 12mm trocar, provides limited control, not suitable for bowel retraction (bowel may slip from retractor)
ExtraHand™ (Medtronic) 	Soft inflatable end, cheaper than EndoPaddle, designed for open surgery and/or laparoscopy	Limited contact area and control of the bowel, risk of tissue slipping, requires an operator, 10 mm port required
LapSpace (LapSpace Medical) 	Rake-like shape to retract the bowel, soft inflatable interface, may be clamped to bedside	Little manoeuvrability, relies on retraction very close to the operating space, reduced surface contact area

3.4.3. Competitive Advantage

In a response to the present unmet need for safer bowel retraction, SecuRetract has been developed as previously described to overcome the weaknesses of currently available device. Figure 3.25 highlights the four principal design advantages of the SecuRetract device.

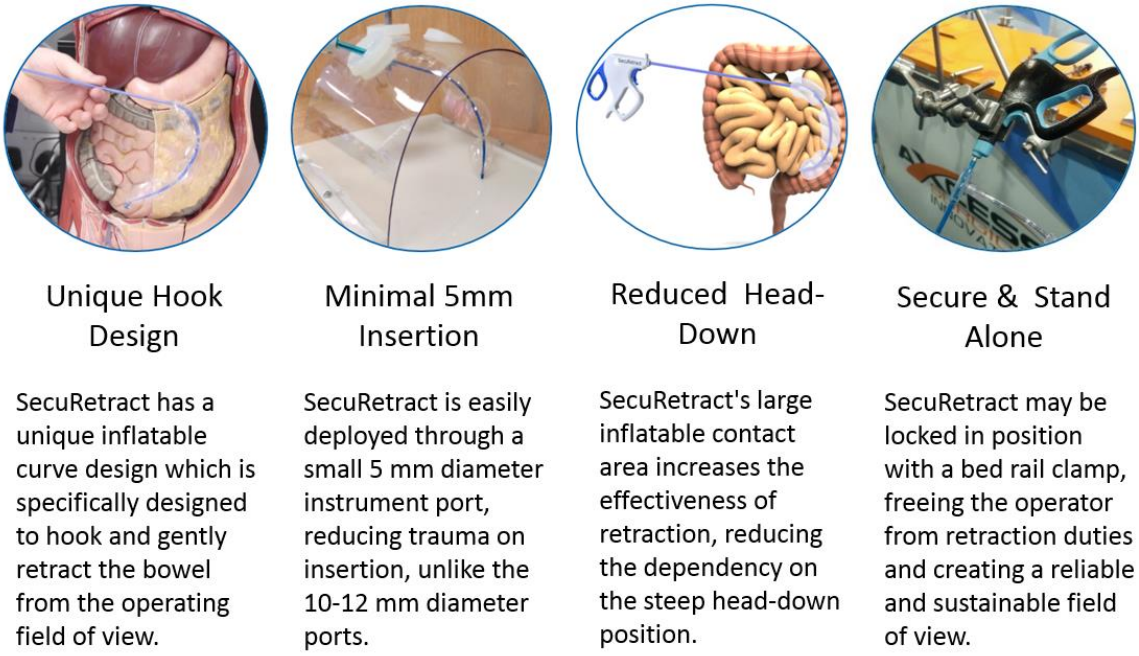


Figure 3.25 Key design advantages of SecuRetract

A Design Failure Mode and Effect Analysis was carried out as part of the Risk Management operating procedure developed as part of this work in line with ISO 14971. Following the potential sources of failure listed in appendix C of ISO 14971, the most severe risk level identified was level two (see Section 2.4.1). These risks relate to potential device failure relating to misuse or inadvertent contact with auxiliary devices such as a diathermy used to cauterise tissue. The potential clinical effect caused by malfunction is the release of the bowel resulting in unexpected migration into the operating field disrupting the procedure. However, the risk of inadvertent rupture is common to all inflatable devices and is typically mitigated through robust design of materials and effective communication of device intended use and instructions for use. Other potential risk which are common to all medical devices involve sterility, incorrect labelling, and adequate which are overcome thought he implementation of quality and process controls.

3.4.4. Key Opinion Leader Feedback

Over the project lifetime, SecuRetract prototypes have been presented to over fifty surgeons across Europe and the USA. SecuRetract was presented to surgeons at the Cleveland Clinic, Massachusetts General Hospital, Brigham and Women's hospital, the European Colorectal Congress (ECC), Stanford Medical Centre, SAGES surgical conference and to a host of Irish physicians. During the course of the ECC in Munich, 24 surgeons were individually surveyed on the immediate use of SecuRetract in their clinical practice [6]. The author procured a stand in the exhibition hall of the ECC and engaged with surgeons who were willing to complete a questionnaire. The experience of those surveyed ranged from newly appointed surgical physicians to established surgeons in their late fifties. The principal results of the survey are as follows:

- Of the 24 surgeons surveyed 67% would use SecuRetract immediately (Figure 3.26).
- A further 25% would like to use SecuRetract pending further clinical data.
- Two respondents (8%) specialised in open procedures did not see a need.
- Over half of those surveyed said they would use SecuRetract at least once a week (approximately 1 in 3 procedures).
- Colectomy (95.5%) and rectal (72.7%) surgery are the most immediate applications.
- Other indications include bariatric surgery (36.4%) and gastrectomy (22.7%).
- Sixteen European surgeons signed up to use SecuRetract when available.

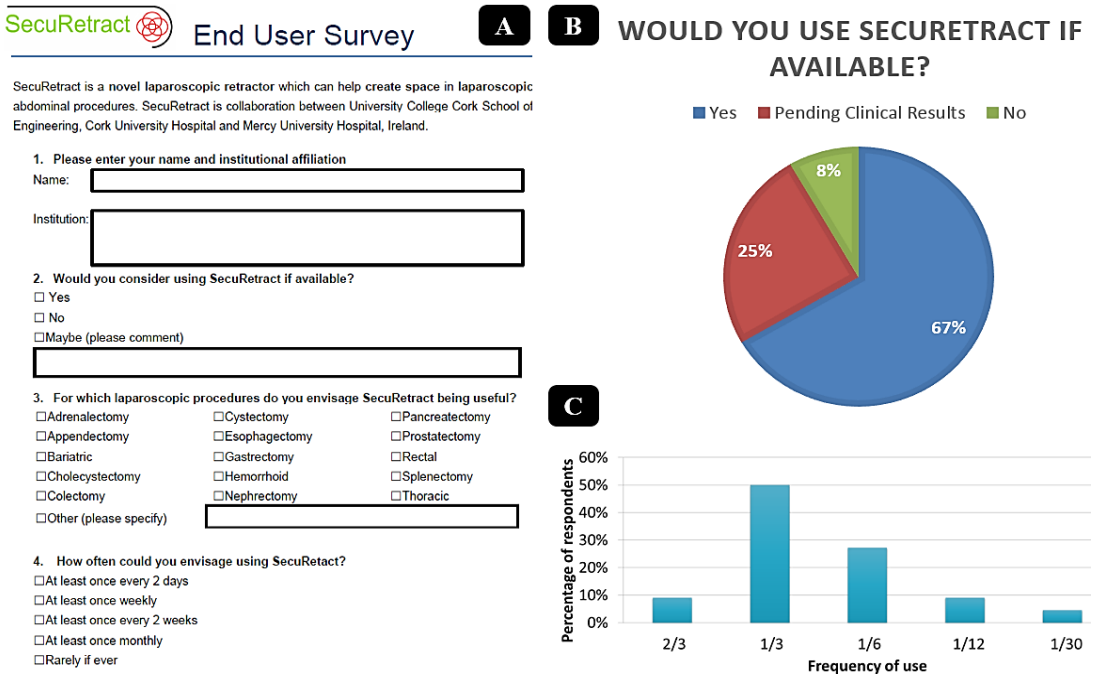


Figure 3.26 Colorectal Congress results [6]**: A) Example of part one of the survey, B) feedback on usability of SecuRetract, and C) feedback on frequency of use of SecuRetract.**

SecuRetract was also presented to a number of US and Irish clinicians during one-on-one interviews during the course of this research. A summary of the key points from three selected interviews are listed in Table 3.3.

Table 3.3 Feedback from key opinion leader in the US and Ireland.

Clinician	Feedback
Prof. Hermann Kessler, Colorectal Surgery Cleveland Clinic, Ohio	Prof. Kessler thoroughly examined the prototype. The handle design felt comfortable and easy to use. He especially liked the balloons creating a soft interface with the internal organs. It was noted that SecuRetract would not be used for every procedure but would be of particular use in cases where gravity alone is not sufficient to retract the bowels (approx. 1/3). Prof. Kessler offered to test SecuRetract as soon as there is a prototype is available. He also showed the device to a few of his colleagues who were also interested in testing SecuRetract and remarked favourable on the articulation and soft design features.
Prof. Cindy Kin, Professor of Colorectal Surgery, Stanford Medical Health Centre	Prof. Cindy immediately liked SecuRetract, noting that there is nothing like it currently on the market. Cindy was particularly impressed with the balloons and the curved shape. Cindy was immediately able to use the device with little or no instruction. The size and shape fitted perfectly. It was remarked that it felt like other devices in terms of operation, and the size and feel of the handle was very comfortable. Cindy noted that the benefits include "reduced surgeon frustration". One of the most frustrating parts of colorectal surgery is using table tilt. Often the patient has to be restrained to avoid slipping. Reducing table tilt will greatly improve patient safety as well as reducing surgeon frustration. Interestingly Cindy noted that she would be tempted to use SecuRetract in open surgery to overcome the frustration of trying to hold back the bowl.
Prof. Ronan Cahill, Professor of Surgery Mater Misericordiae Hospital and University College Dublin	Prof. Cahill liked the very elegant and ergonomically pleasing design. He envisaged using the device in laparoscopic colectomy and rectal procedures although his own use of the device would be limited to a few cases. He saw a greater need in developing markets where surgeons would be less experienced in laparoscopic surgery. He indicated willingness to be part of initial clinical investigations with the device at Mater Misericordiae University Hospital.

3.4.5. Intellectual Property Review

As part of the Masters research described in Section 3.2.1, a preliminary European Patent was filed for SecuRetract on the 21st December 2012. During the course of this PhD research, an international PCT was filed before SecuRetract entered into the nationalisation phase with filings in both Europe and the USA in 2015.

The author worked with the university technology transfer office to publish each phase of the IP process. Subsequent to a European patent filing at PCT phase, an international search report and written opinion is generated by the European Patent Office. The search report provides an opinion on the inventiveness and novelty of the proposed invention as well as providing an opinion on the overall unity of the application and associated claims. In the case of SecuRetract, the search report recognised the novelty and inventiveness of SecuRetract. However, the report also identified a number of claims which were determined as being too close to previously disclosed inventions and thus for the final utility filing, the number of claims were reduced to remove any potential infringements. The final novel claims focused on protecting the actuation and inflation of the distal end which is unique to the SecuRetract device.

3.4.6. Regulatory Feasibility Review

Europe:

SecuRetract was classified as a Class IIa device via classification rules defined within the Annex IX of European Directive 93/42/EEC as amended, and schedule 9 of related Irish regulation (S.I. No. 252/1994), and in particular to rule seven pertaining to surgically invasive devices for short term use. As a Class IIa device there are a number of conformity assessment routes feasible for the SecuRetract device. This includes the application of Annex II, EC Declaration of Conformity (Full quality assurance system). Annex II requirements include the following:

i. Declaration of Conformity by the manufacturer,
ii. An assessment by a Notified Body of the manufacturer's Quality System versus the requirements of EN ISO 13485:2012,
iii. Compilation of a Technical File for examination of the product design by a Notified Body.

CE marking in accordance with Annex II is feasible for the device with a Technical File derived from within an EN ISO 13485 certified Quality Management System. The Essential Requirements Review must reference, and the Technical File must contain a "Clinical Evaluation" Report. This report should include a clinical literature evaluation of reputable clinical articles that demonstrate the prevalence and relative safety of laparoscopy retractors on the market.

Providing adequate data is provided in a format that conforms to the Manufacturers and Notified Body's Guidance MEDDEV. 2.7.1, it is likely that the legal manufacturer's selected Notified Body will accept the safety and effectiveness of the device without the need for human trials. Considering the invasive nature of the device it is conceivable that the legal manufacturer may be required to pro-actively commit to collecting information on quality, safety or performance of the Medical Device after it has been placed on the market.

United States:

For FDA Classification guidelines, a device which falls within the controls of product Code GCJ, associated with endoscope and accessories (FDA regulation number 876.1500), may be deemed as a Class II device. Therefore the submission type is 510(k) as determined in Product Code GCJ.

In order to successfully submit a 510k application for SecuRetract, the device must be proven to be "substantially equivalent" to one or more existing approved devices on the US market. It is apparent that numerous devices with the same product code and similar intended use are already approved on the US market. Devices such as the A-Lap™ retractor (EZsurgical, 510k application K082291) and the ExtraHand™ balloon retractor (Medtronic, 510k K962005) have been identified.

Design verification and design validation data derived within a 21 CFR Part 820.30 Design Control process will be necessary to determine and demonstrate the equivalence of SecuRetract to one or more predicate devices. On the basis that at least x10 potential predicates exist, including devices with similar technology, a US 510k application for SecuRetract will be feasible and is deemed an appropriate regulatory pathway. The 510k application will be subject to FDA review prior to approval.

Providing adequate data is generated to demonstrate substantial equivalence with predicates it is unlikely that human trial data will be necessary to support the pre-market approval 510k application. This is ultimately at the discretion of FDA reviewers but it is a relatively low risk to this pathway considering the prevalence of predicate devices on the market. Any potential patient risks can be assessed and mitigated by applying the FDA recognised standard ISO 14971:2007 with the Design Control process and by supporting the application with a Clinical Evaluation Report, including a Clinical Literature Review.

3.5. Chapter Review

An essential part of any laparoscopic surgery is to ensure that the surgeon has sufficient exposure to visualise the operating field and surrounding structures to perform an effective and safe procedure. Laparoscopic retraction has advanced greatly since it was first introduced in 1991, yet a safe and effective laparoscopic retractor has yet to be universally acknowledged [52], [82]. Through an iterative design process and continual consultation with end users, SecuRetract was developed. The presented solution has the potential to displace currently available laparoscopic retraction devices due to a number of key operational and performance advantages.

3.5.1. Technical and Commercial Review

The main proposed advantage of SecuRetract over alternative deployable retractors is that it can be adjusted and manoeuvred to suit any lower abdominal surgery. The device may be inserted through a 5 mm diameter port which, in turn, reduces recovery time when the facial defect (incision) is closed post-surgery. The inflatable nature of the device negates the risk of tissue perforation, and the cylindrical balloons increase the surface area with the bowel wall reducing contact pressure. Due to the unique mesenteric hook profile, SecuRetract can retract a far larger section of the bowel compared to the traditional laparoscopic retractors discussed in Section 3.1.2. Therefore, laparoscopic surgery may be undertaken at a reduced Trendelenburg position (less head-down). This will reduce intra-operative complications, reduce operational time, and consequently, decrease hospital costs. In addition, SecuRetract offers improved ease of laparoscopic access by means of its rapid deployment and retraction through a single 5 mm diameter port. This feature is particularly amenable for extending the device's use to clinical indications outside of colorectal surgery (e.g., upper gastrointestinal interventions). The curvature and length of the shaft may also be altered to provide a selection of SecuRetract devices as appropriate to a specific procedure.

While the results of this preliminary analysis, experimentation and end-user feedback are encouraging, a clinical investigation will be required to investigate the efficacy of small bowel retraction in the supine position and comparing same to commercially available techniques. Results from the pre-clinical investigation have led to a number of design improvements which have enhanced the operational performance and ease of use over the course of this PhD. As a result, the current solution points to a promising

alternative laparoscopic retractor to improve surgical access and to help alleviate complications during laparoscopic colectomy and hysterectomy.

3.5.1. SecuRetract Design Control Review

The laparoscopic retraction project began before the implementation of the quality management system, therefore the design control framework had little influence over the early stages of development. Despite this, the author had recognised the stage-gate approach early into this PhD work and throughout the development of SecuRetract, the main milestones were targeted prior to formally describing same in a controlled procedure. All records were maintained of all design development activities which were subsequently used to retrospectively populate the project's Design History File. One limitation with the verification of medical devices in general, is that all verification protocols to be included in the regulatory submission, have to be completed under good laboratory practices in order to assure accurate results. This presents difficulties to small research groups who may not have access to such resources. Further financial investment is required to support these actions which will be addressed by the licenced company responsible for commercialisation.

The author found the implementation of quality controls to be time consuming and quite burdensome. In particular, it was difficult to maintain and catalogue routine design meetings and design iterations as often new ideas and improvements came through unscheduled discussion with practitioners or experimental testing. In the case of the SecuRetract project, all the design documents such as the Design and Development Plan, were retrospectively populated. Therefore the plan reflects what was achieved rather than setting goals and timelines from the beginning. Furthermore much of the design history file is still being populated and will not be completed until the device is finally ready for design transfer in Phase 4 of the design control process. As discussed above, much of the final activities are subject to further funding to access the appropriate resources. However, once a completed design quality system has been established and evaluated through the development of several projects, the author appreciates that such a roadmap to design control and development will be invaluable.

The control process will serve to frame the project output requirements and to determine the essential steps towards clinical adoption and regulatory approval. The author does recognise that a dedicated quality controller may be required to ensure

compliance and to routinely schedule review meetings which often may be more difficult than anticipated owing to the busy nature of university staff and clinical advisors. On reflection, had this project been prospectively implemented into the deign control process rather than retrospectively, the author believes that more focus would have been placed on design for manufacture at an early stage and that the overall timeline would have been significantly reduced by following a clear and focused development plan. SecuRetract is currently in Phase III of the project design and development cycle, as described in Chapter 2. Table 3.4 qualitatively estimates the progression of each stage gate activity. The outstanding actions left in Phase III involve finalising production processes, and to build production units to undertake design verification and validation activities.

Table 3.4 SecuRetract project progression.

	Phase I	Phase II	Phase III	Phase IV	Phase V
Phase Activity Completion	Clinical Need Definition	Design and Development Plan	Detailed Requirements Specifications	Design Transfer / Pilot Production	limited Market Release
	100%	100%	80%	0%	0%
	Concept Solutions / Early Risk Assessment	Define Design Inputs	Manufactures / Suppliers Identified	Final Design Validation	Post-Market Surveillance
	100%	100%	80%	0%	0%
	Early Commercial / Market Assessment	Initiate Quality Documentation	Risk Assessment Update / Implement Risk Controls	Complete DHF, DMR, Technical File	Sales and Physician Training
	100%	100%	75%	25%	0%
	Early Intellectual Property Review	Build and Evaluate Prototypes	Verification & Validation Protocols	Artwork / Traceability	Expand Sales Effort
	100%	100%	50%	50%	0%
	Early Regulatory Assessment	Expanded IP landscape Review	Build Units for V&V	Market Launch Strategy	Continuous Improvement
	100%	100%	50%	75%	0%
		Risk Analysis Update	Process Validation Plan	Manufacturing Qualification	Quality Audits
		100%	0%	0%	0%
		Define Regulatory Requirements	Confirm Intellectual status	Regulatory Approval	
		100%	90%	0%	
		Business Plan	Update DHF / Business Plan	Build Inventory / Scale Up	
		80%	50%	0%	

Chapter 4 ProDural: Enabling Safe Epidural Placement

Epidural analgesia is a form of regional analgesia involving the careful placement of a needle tip into the narrow epidural space between the spinal dura and the ligamentum flavum, and the subsequent injection of drugs through a catheter placed into the epidural space. Epidural administration is the standard therapeutic method for pain relief during labour and has changed very little since it was first introduced at the start of the twentieth century. However, with a very steep learning curve and relatively high failure rates among trainee anaesthetists, the current method is not ideal. This chapter presents a possible solution to improve the safety and efficacy of epidural administration. The proposed solution, developed as part of this PhD, is consistent with traditional methods and comprises an additional visual indicator to signal successful placement.

4.1. Background and Clinical Need

The clinical need for which this project is based on was presented at the 2012 UCC BioDesign module by Dr. Peter Lee, Consultant Anaesthetist at Cork University Hospital. As an undergraduate at the time, the author was a member of the original team tasked to produce an early stage solution. Aside from referencing the concept from the BioDesign module, all work described within this chapter was conducted by the author as part of this PhD. In the context of the design control process, this project has advanced to Phase III. The following sections will detail the clinical need to improve epidural administration as the principal application, and an alternative clinical indication associated with creating a pneumoperitoneum during laparoscopy.

4.1.1. Epidural Administration

Epidural administration of local anaesthetic and/or opioids is performed for analgesia and anaesthesia in the perioperative or peripartum period or to provide analgesia before surgical procedures and labour. It is also commonly used as a therapeutic method for pain relief. The US Department of Health and Human services reported that 70.85% of births in the US in 2011 involved epidural or spinal anaesthesia. This amounts to approximately 2.76m deliveries involving the provision of epidural/spinal anaesthesia during labour. Epidurals block the nerve impulses from certain spinal segments resulting in decreased local sensation. Although epidural anaesthesia has been part of anaesthetic practice since 1901, localisation of the epidural space remains technically difficult [83]. Epidural analgesia has been described as the gold standard of pain control [84].

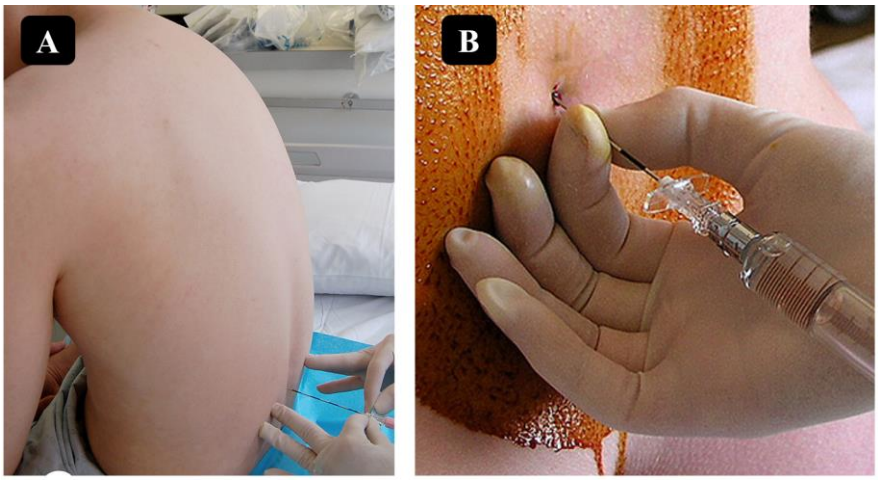


Figure 4.1 A) Initial positioning of epidural needle between protruding spinous processes, and B) advancement of epidural needle using the loss of resistance technique.

The technique requires a clinician to blindly pass a needle through soft tissue and ligament between the caudally protruding spinous processes of the vertebrae. Confirmation of needle tip entry to the epidural space is most commonly achieved by the loss-of-resistance (LOR) technique; a sudden, yet subtle, pressure drop at the needle tip which is sensed at the syringe plunger. The needle is grasped with the non-dominant hand and pushed toward the epidural space while the dominant hand (thumb) applies either constant steady pressure, or pulsing intermittent pressure on the syringe plunger. Once the epidural space is entered, the pressure applied to the syringe plunger allows the syringe medium, which may be air or saline or a mixture of both, to flow without resistance into the epidural space [85]. Once the operator detects the LOR and is satisfied that the epidural needle is in place, the syringe is removed and a catheter is threaded through the needle into the epidural space. Finally the needle is carefully removed, leaving the catheter in place to provide medication either through periodic injections, or by continuous infusion.

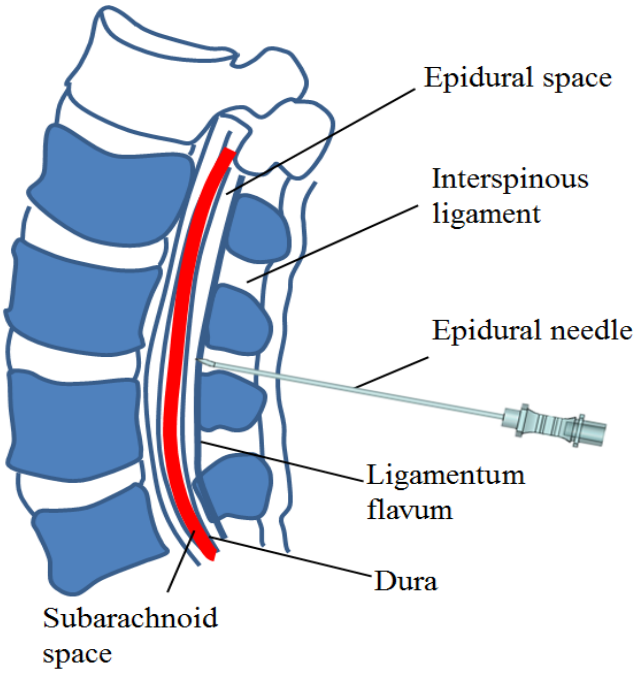


Figure 4.2 Graphical representation of the epidural space and surrounding anatomy with an epidural needle tip positioned in the epidural space.

The epidural space is a very thin layer located between the interspinous ligament and the subarachnoid space which in turn is protected by the dura mater (see Figure 4.2). The ligamentum flavum is a dense layer of tissue located immediately before the epidural space and presents the greatest resistance to needle advancement. The midline approach

is a common method for needle advancement and involves orientating the needle until it is orthogonal to the patients back and advancing the needle through the interspinous ligament and finally the ligamentum flavum. In 2009, Tran *et al.* [86] estimated the average force and syringe pressure required to penetrate the ligamentum flavum in a human subject using the continuous pressure technique and the midline approach. It was found that the force and pressure applied in the ligamentum flavum was significantly higher than the interspinous ligament (see Table 4.1). The estimated pressures were calculated to be around 37.5 ± 20.0 kPa for the ligamentum flavum and 15 ± 5.3 kPa for the interspinous ligament [86]. These pressure values were assumed as operational pressures for future designs.

Table 4.1 Penetration force and estimated pressures for human subjects while advancing an epidural needle using the midline approach [86]**.**

Region	**F_{avg} (N)**	**F_{max} (N)**	**P_{avg} (kPa)**	**P_{max} (kPa)**
Interspinous Ligament	2.0±1.4	4.6±1.3	15.5±12.0	34.9±17.4
Ligamentum Flavum	5.0±3.0	6.0±3.0	31.5±28.0	39.5±30.3
p-value	<0.05	<0.05	<0.05	>0.25

4.1.2. Epidural Failure

Accidental dural puncture (i.e., entry into the subarachnoid space) is the most significant complication associated with regional anaesthesia but the incidence is hugely dependent on clinician experience. For experienced clinicians puncture rates are typically between 1-3% [87]. However, for trainee anaesthetists, the mean epidural failure rate is one in every five consecutive epidurals for the first 50 epidurals performed [88] (see Figure 4.3). Proficiency in the loss-of-resistance technique is difficult to teach or demonstrate. As many as 60 attempts at epidural anaesthesia may be required before a 90% success rate is achieved [89], [90]. The technique may also be unreliable in patients with altered vertebral anatomy or calcified spinal ligaments, while epidural anaesthesia failure rates are greater in obese patients [91]. There is an urgent need to provide confirmation of epidural entry for these novice end-users. The most benign consequence of these so-called ‘spinal taps’ is severe and prolonged headaches for the patient which occurs in approximately 86% of accidental dural puncture. Patients with severe post-dural puncture headaches may be readmitted and treated with an epidural blood patch leading to additional insurance and healthcare costs [92].

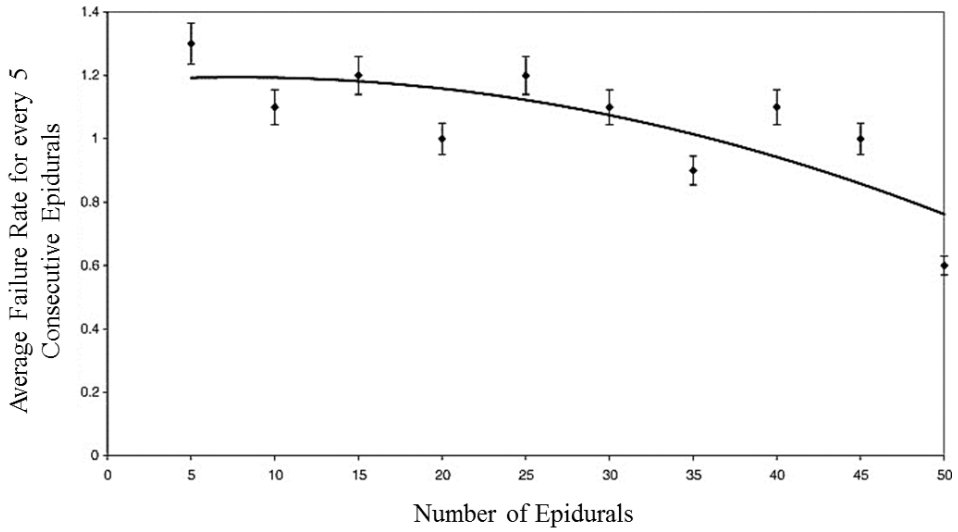


Figure 4.3 Epidural failure rate for every five consecutive epidurals taken from Dashfield *et al.* (2000) [88]**.**

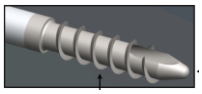
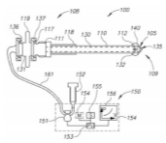
A more common complication of epidural administration is a 'false positive'. Based on haptic feedback, the clinician incorrectly assumes the epidural space has been reached. This is more likely to occur in obese patients due to air or saline leakage as the epidural needle passes through layers of fatty tissue giving false LOR feedback. In rare circumstances (<1% [93]), complications associated with the current LOR technique may also include pneumocephalus, spinal cord and nerve root compression, subcutaneous emphysema, venous air embolism, and neurological injury [83].

4.1.3. Current Solutions and Technology

The regional anaesthesia global market is dominated by a small number of players with three brand leaders in the US; Perifix® (B.Braun, Melsungen, Germany), Portex® (Smiths Medical, Kent, UK) and Epilor™ (Becton Dickinson (BD), Franklin Lakes, NJ, USA). In the UK, Portex has a dominant position with an estimated 85% epidural market share. The most prevalent technology is the loss-of-resistance (LOR) syringe. Polyproplyene LOR syringes are cheap to manufacture and represent the single largest competitor. In 2006, 99% of anaesthetists in the U.K. used some form of the LOR technique to identify the epidural space, be it a continuously applied pressure or a pulsing, intermittent pressure to the syringe plunger (LOR to saline continuous 58%, saline intermittent 16%, air continuous 4% and air intermittent 21%) [94]. In recent years, developments such as fibre optics [95], ultrasound [96], products such as Compuflo® (Milestone Scientific, Livingston, NJ, USA) [97] which employs sensors to detect the pressure drop and the Acoustic Puncture Assist Device (Equip Medikey, Gouda,

Netherlands) [98] have been developed to replace the conventional manual LOR technique. However these high end alternatives have struggled to achieve market penetration due to expensive up-front investment and lack of clinical inertia. A list of selected commercially available epidural devices are listed in see Table 4.2.

Table 4.2 List of epidural administration technology.

Product	Supplier	Description	Disadvantages of Product
LOR Syringe 	Multiple	Low cost, single use. LOR technique. Clinical gold standard. Ease of manufacture.	Relies exclusively on haptic feedback to determine if needle tip has entered the epidural space leading to a steep learning curve and operative complications.
Episure 	Indigo Orb Inc. (US)	Single use. Does not use the LOR technique. Low cost. Spring loaded.	Difficult to detect false positives, and there is a chance of the spring loaded mechanism going off prematurely.
Epidrum 	Exmoor Innovations (UK)	Single use. Syringe attachment. Localise epidural space by means of a visual signal. Does not maintain LOR technique.	Additional steps to assemble the syringe-Epidrum-needle configuration. Risk that the needle will become blocked with tissue.
Epiphany 	InSite Medical Technologies (US)	Single use. Screw-based needle for securing to surrounding tissue. No visual indicator. Does not maintain LOR technique.	Relies on a slow and delicate screwing process. Risk of tip getting blocked with matter. Presents a complete shift in technique from the LOR method.
Opeq 	Opeq Medical	Sensor-based technology for monitoring pressure variation on entry.	High-cost solution which relies on electronic sensors to confirm entry.

A number of these devices still avail of the pressure drop technique which include Episure™ (Indigo Orb, Irvine, CA, USA) [99] and Epidrum® (Exmoor, Somerset, UK) [100] (see Table 4.2). Both of these devices are "charged" prior to application and automatically retract once the epidural space has been reached. However, instead of the user receiving a tactile feedback, these devices provide solely visual

confirmation when the epidural space has been reached, thus creating uncertainty of correct needle placement. Other emerging devices include Epiphany and Omeq are not yet commercially available but represent significant differences from current clinical best practice and are therefore expected to face significant resistance towards adoption based on end-user feedback. Epiphany relies on slowly advancing the blunt needle tip towards the epidural space by using the threads to produce a controlled forward screw like motion.

Syringe solutions such as Episure and Epidrum have struggled to gain market penetration. The National Maternity Hospital Holles Street (Dublin) suspended any future trials on the Epidrum device due to false readings. Both devices discharge slowly as they pass through the low density fatty tissue and are difficult to recharge.

4.1.4. Laparoscopic Pneumoperitoneum

Another potential application of a natural cavity detection device is to identify the abdominal cavity to create a pneumoperitoneum (the introduction of gas to create space in the peritoneal cavity) in advance of minimally invasive surgery. This task is currently completed using a trocar or a veress needle (see Table 4.3). A trocar functions as a portal during laparoscopic surgery to insert instruments and to create a pneumoperitoneum. Trocar insertion has been identified as the most dangerous risk of laparoscopic surgery. Despite advances in trocar technology, the creation of a pneumoperitoneum along with insertion of trocars remains the source of significant injuries to the wall and vasculature [101]. The overall incidence of major vascular injury due to trocar and veress needle entry is 1.1/1000 [102] and constitutes 1/5 of all medical insurance claims associated with laparoscopic surgery [101].

Figure 4.4 Trocar Placement through abdominal wall [174]**.**

Several studies [103]–[105] suggest that the initial trocar insertion is the most dangerous aspect of trocar use, and possibly the most dangerous step in minimally invasive surgery. Champault (1996) [104] found that 83% of vascular injuries, 75% of bowel injuries, and 50% of local haemorrhage injuries were caused during primary trocar insertion. Unfortunately, a large fraction of trocar injuries are not diagnosed at the time of injury. Krishnakumar (2009) [24] reports that some 30-50% of bowel injuries and 13-50% of vascular injuries are undiagnosed at the time of surgery. The mortality rate from

bowel injury is between 2.5-5% [25] and the mortality rate for all bowel and vascular injuries is between 3-30% [108].

There are three common clinical approaches for initial trocar placement during laparoscopic surgery. The open or Hasson technique involves insertion of a Hasson cannula which allows insufflation during laparoscope entry. The closed technique involves blindly inserting a Veress needle (a spring loaded needle) followed by insufflation and trocar insertion. The direct entry technique involves immediate and blind entry with a trocar. While direct entry reduces procedural time, the three techniques have comparable rates of complication and all three are widely practiced depending on surgeon's preference [109]. It is estimates that 40% of surgeons use (closed) Veress needle insufflation prior to primary trocar insertion, while 30% use a direct (no insufflation) trocar insertion method and 30% use the Hasson method [110].

Table 4.3 List of surgical technology used to establish a pneumoperitoneum.

Product	Supplier	Description	Disadvantages of Product
Shielded trocars 	Multiple	Low cost, single use. Outer shield reduces initial puncture pressure.	Initial blind puncture risk. No evidence of lower injury rates with shielded trocars.
Radially expanding sleeves 	Covidien (US)	Single use. Blunt tip may reduce risk of abdominal wall injury	Significant additional force required compared to disposable trocars.
Optical trocars 	Ethicon (US) Covidien (US) Stortz (Ger)	Reusable and single-use available. Facilitate laparoscopic visualisation during insertion.	Optical trocars require initial Veress needle insertion and do not reduce risks associated with gas embolism.
Veress Needle 	Multiple	A spring-loaded needle used to create pneumoperitoneum for laparoscopic surgery	Can lead to vascular and organ perforation. Not as commonly used as a trocar.

4.2. Design Definition and Evolution

Two clear unmet clinical needs have been described. When broken down to an engineering problem, the issue involves the detection of a cavity (be it the epidural space or peritoneal cavity) beyond a dense penetrable membrane (posterior tissue or abdominal cavity). The design process focused on the clinical application of epidural administration as this was seen as the greater clinical need. The following sections will describe the design iteration process; initially during the BioDesign module and subsequently as part of this PhD thesis, while focusing on a defined clinical need.

4.2.1. Problem Statement

To develop a means of improving the accuracy and safety of detecting the epidural space during epidural administration which can reduce the risk of intraoperative complications, reduce the incidence of false positives, and offers a cost effective, user friendly solution.

4.2.2. Design Criteria

A list of design criteria was derived from end-user surveys, literature reviews and competing technology assessment. The resulting requirements were subsequently considered during the design process. These requirements include a solution which:

1. Consistently and reliably informs the operator when the needle tip has entered the epidural space.
2. Is light-weight, durable, easy-to-use and requires minimal set-up, to cope with the practicalities of everyday clinical practice.
3. Maintains the existing LOR techniques with minimal time lag between detection and conveying the information to the user as the distances involved are small.
4. Reduces the steep learning curve.

4.2.3. BioDesign Solution

The original concept, which was developed as part of the author's BioDesign group, comprised a modified LOR syringe and an attachable pressure drop detector. The attachment provides an additional visual signal that the epidural space has been reached (see Figure 4.5).

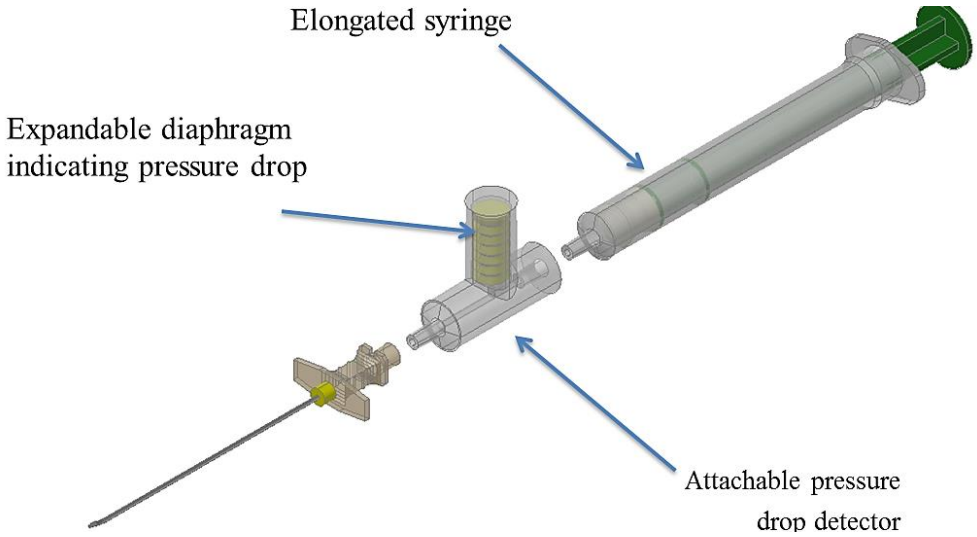


Figure 4.5 Original solution developed as part of the BioDesign Module illustrating the detachable pressure drop detector and modified syringe.

The proposed solution operated on the same principle as the existing LOR syringe (see Figure 4.5). The pressure drop detector, which further comprised an expandable diaphragm (bellows), is inserted between the syringe and Tuohy needle (a needle design commonly used to locate the epidural space with a curved tip). As the needle is advanced towards the epidural space and pressure is applied to the plunger, the diaphragm rises upward. Once the epidural space is reached, the diaphragm will collapse as the air or saline solution used to charge the barrel exits the syringe through the needle. The collapsing mechanism acts as secondary visual confirmation that the epidural space has been reached.

However, the BioDesign solution included a number of limitations that needed addressing. The bellows-actuated visual indicator presents manufacturing difficulties and may pose operational limitations depending on the orientation of the bellows (i.e., if suspended upside down, would the internal pressure be sufficient to overcome the effects of gravity). Further design development was therefore required as well as assessing the market size and end-user demand.

4.2.4. PhD Design Evolution Overview

The epidural project was included as one of the devices to develop further within this PhD research. The original concept, albeit not technically viable, did present an interesting concept to include a visual indicator to improve epidural administration. One of the first actions was to carry out a more expansive review of the Intellectual Property Landscape (i.e., Phase I of the Design Control Process). It was here that the

author identified the EpiDrum device (see Table 4.2) which presented cause for concern from an intellectual property perspective [100]. To that end the design criteria was expanded to include a device which incorporates a built-in pressure drop detector which removes the assembly process of EpiDrum and is specifically designed to enable both continuous and pulsing loss-of-resistance techniques.

The design cycle followed an iterative process looking at different mechanical means of detecting a pressure differential. The solutions were subsequently rendered using SolidWorks (Dassault Systèmes SolidWorks Corp., Waltham, MA, USA) and developed in-house using rapid prototyping technics such as 3D printing to assess their potential merits of meeting the design criteria (see Figure 4.6).

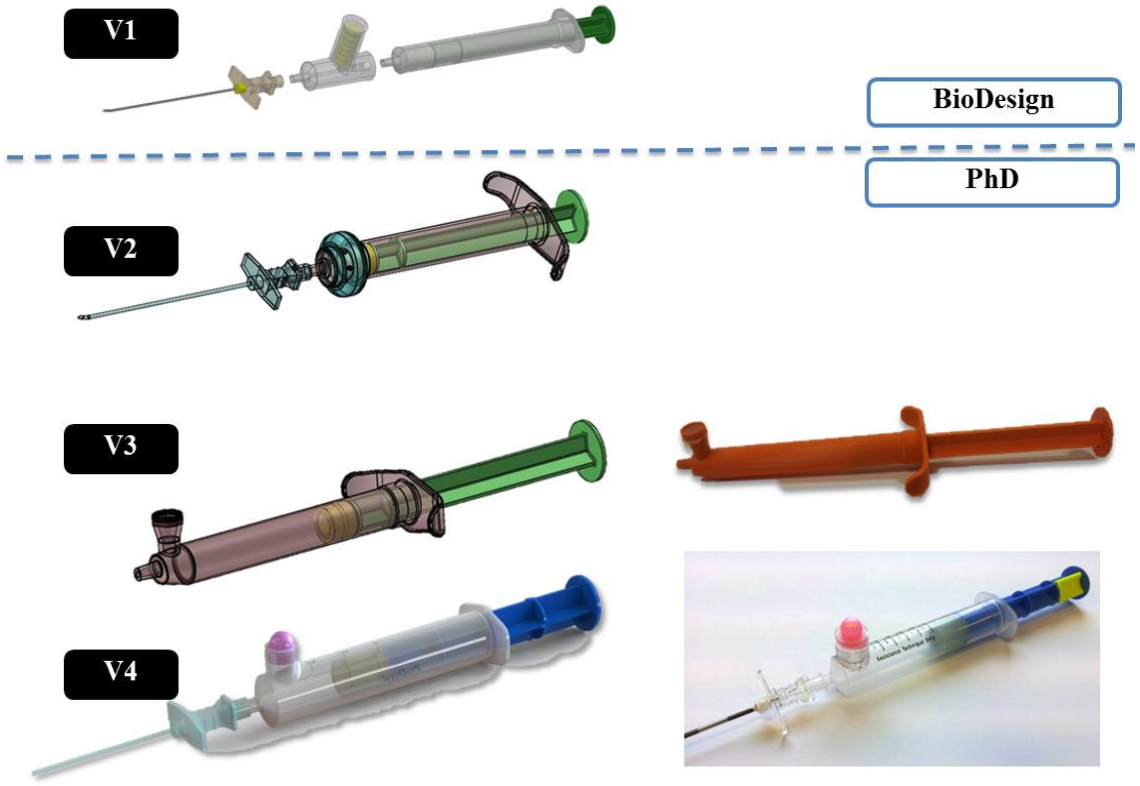
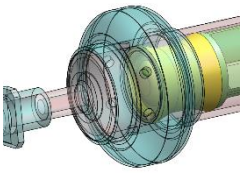
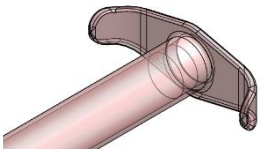


Figure 4.6 Concept iteration: V1 original solution from BioDeisgn module, V2 radially expanding balloon on distal end, V3 chimney design with expandable membrane, and V4 final design iteration.

Similar to the SecuRetract project, inflatable technology was used to provide a cost effective and functional method of detecting a pressure differential. Each design was prototyped and presented to clinical advisors for feedback. The principal design reasons for each iterative advancement are summarised in Table 4.4

Table 4.4 ProDural revision history summary.

Rev	Description of Current Design	Reason for Design Change
V1 to **V2**	V1 is reflects the BioDesign concept. Attachable visual indicator with expandable bellows.	Design for manufacture of the bellows not practical. Potential infringements of the EpiDrum device IP.
V2 to **V3**	V2 comprises a radially expanding, elastomeric cuff, located at the distal end of a modified syringe. Provide 360º axial rotation visual confirmation of pressure increase with plunger advancement. Epidural space localisation confirmed through collapse of cuff.	Excess volume on inflation (>40 mm^3). Risk of over injection of air / saline on locating epidural space. Dilation balloons have a high cost of production and requrie balloon moulds. 
V3 to **V4**	Finger slot design presented in V2 retained in V3. Movement to chimney design with more cost effective, expandable elastomeric disk design.	Finger slot removed. Risk of catching user's finger during use and dislodging epidural needle tip from space. 
V4	V4 illustrates an improved chimney design with to accommodate injection moulding as well as a snap cap design to house and secure elastomeric diaphragm.	

The final design, V4, provides both visual and haptic feedback of needle entry into the epidural space and is consistent with traditional LOR syringes. This is achieved by integrating a visual indicator (inflatable diaphragm) at the distal end of an LOR syringe. By mating the syringe with a needle, the device provides visual confirmation of entry into the epidural space with rapid and immediate collapse of the inflatable diaphragm. This mechanical process results a low cost, and highly manufacturable solution. As part the design control process, a Design Failure Mode and Effects Analyses was carried out as presented in Appendix 4. The following sections will describe the prototype development and evaluation of ProDural's clinical utility.

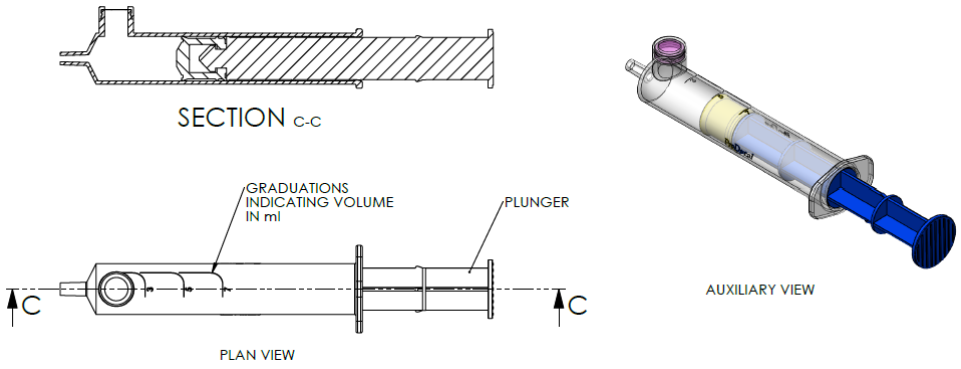


Figure 4.7 Detail of the final ProDural design taken from Appendix 5.

4.3. Prototype Development and Evaluation

In order to demonstrate proof of concept, a minimally viable, functional prototype was required. LOR syringes are manufactured using high pressure injection moulding, usually in polypropylene for both the syringe and plunger and TPE for the plunger cap. Injection moulding is an expensive process for developing prototype grade devices, therefore other rapid prototyping methods were investigated. In-house 3D printing (Dimension Elite, Stratasys) could not produce functional prototypes. A 3D printed barrel would leak air or saline through the porous ABS material due to the layered FDM (Fused Deposition Modelling) process. Therefore, for design evaluation, a standard 7ml LOR syringe was modified (Epilor, BD), to accommodate a visual indicator secured using adhesive epoxy (Loctite).

The visual indicator was prototyped by machining Polymethyl methacrylate (PMMA) rods to varying internal (7.5mm, 10mm, 12mm ID) providing a range of possible configurations (see Appendix 5). The PMMA rods (trade name Perspex) are readily available, cost effective and easy to machine due to its high impact, shatter proof mechanical properties. Material selection for the diaphragm was critical to the development of this device. The material must have be capable of elongation well above 400% as the diaphragm is inflated from a disk to a hemi-spherical shape. For ease of prototyping and first proof of concept, rubber latex was used with varying thicknesses (0.135mm, 0.18mm, and 0.25mm). Latex has a high tear strength with an elongation at break of typically over 800%. The thickness of the latex was measured using a digital micrometre and incrementally stretching the sample in a vice to characterise the variance in wall thickness with planar elongation (see Figure 4.8)

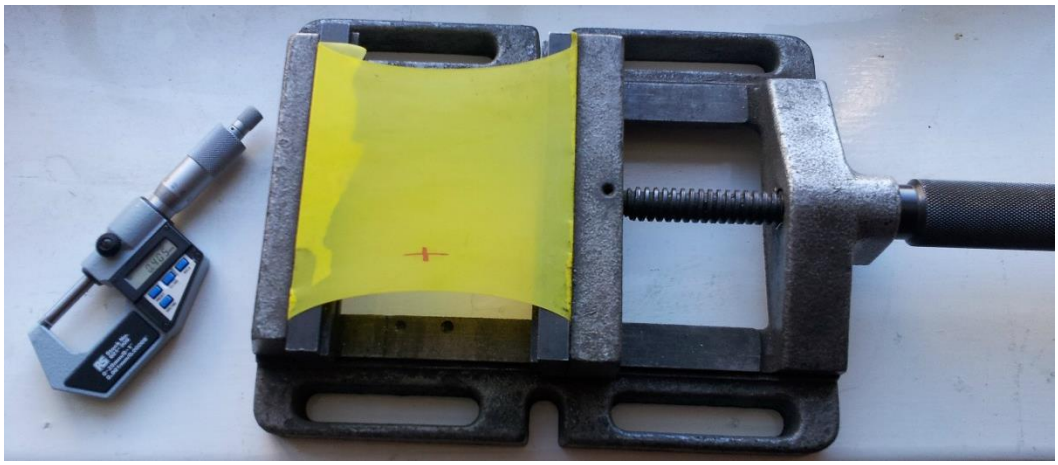


Figure 4.8 Measuring thickness of latex samples.

Two models were used to evaluate the prototypes and provide end-user feedback. The first model was a banana which is commonly used as a model for initial instruction in epidural catheterisation [111]. The proximal, dense surface of the banana represents the patient's skin. As the needle advances and passes through the fruit of the banana it is comparable to the interspinous ligament. Finally as the needle reaches the opposite surface of the banana, the change in density is representative of the needle reaching the ligamentum flavum [9]. The second model was an anatomical mock-up, produced via reverse moulding, with a 3D printer and liquid silicone rubber (Ecoflex® 00-30, Smooth-On, Macungie, PA) (see Figure 4.9). As described in Chapter 3, Ecoflex 00-30 presents material properties similar to soft tissue. The silicone model provides a visual representation suitable for demonstration purposes.

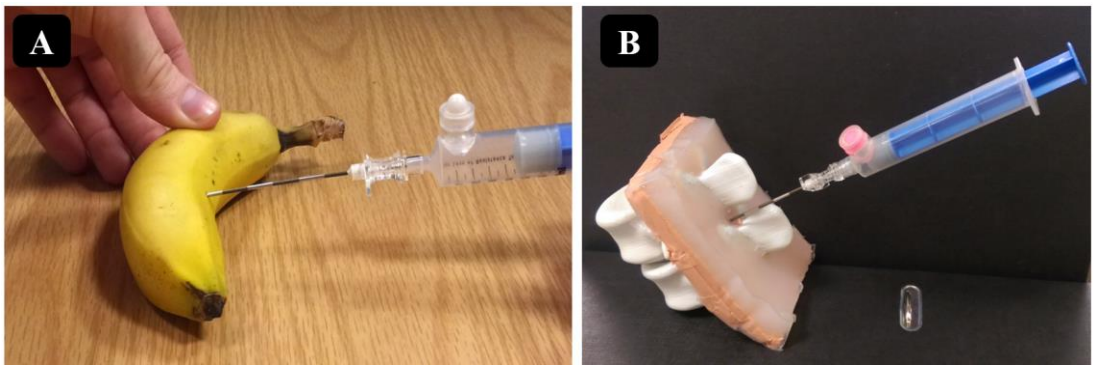


Figure 4.9 A) the banana model used in early proof of concept testing, and B) a rapid prototyped model of a section of the vertebrae with layered varying durometers of silicone simulating interspinous tissue.

Both the banana and silicone models effectively demonstrated the functionality of the initial prototypes. The diaphragm inflation pressure and the immediate responsiveness of diaphragm collapse on pressure drop detection, were in line with the end-users expectations. From this preliminary evaluation, the end user indicated that the thinnest diaphragm (0.135mm) presented the best surface inflation at a familiar plunger pressure (20-30 kPa). In addition, visual evaluation and repeated use confirmed an airtight seal around the diaphragm indicating an adequate snap-fit cap design. These models demonstrated initial technical feasibility. However more in-depth testing was required to fully define the material requirements.

4.3.1. Bench Top Evaluation

To determine the biaxial characteristics of the elastomer diaphragm, the bubble inflation technique was used [112], [113]. The visual indicator is in fluid communication with a pressure gauge and a manual inflation pump (see Figure 4.10).

The bubble inflation pressure was manually controlled by an Encore inflation system (Boston Scientific, Natick, MA). A video camera (resolution of 1980 × 1080 pixels) recorded the inflation pressure corresponding to the bubble height. Experimental assumptions included truly equi-biaxial stretching at the pole of the bubble, uniform thickness at the pole and planar expansion near the rim. It was also assumed that the balloon would display spherical symmetry throughout its expansion. Prior to beginning the experiments, an experienced end-user was asked to blindly determine the typical pressure exerted on the plunger during epidural administration with a conventional LOR syringe. The results, which were captured with a pressure gauge, indicated that the operating intra-plunger pressure range varied from 2 to 5 psig for both continuous and pulsing LOR techniques.

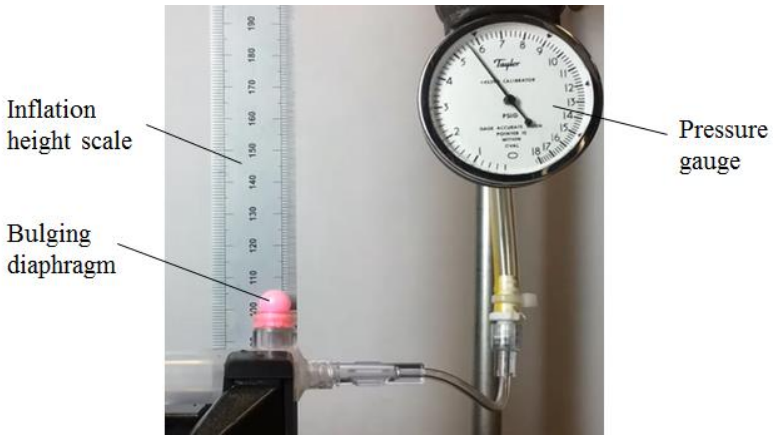


Figure 4.10 Experimental apparatus to evaluate the biaxial characteristics of latex rubber diaphragm at room temperature (21°C).

Three data sets were taken for a 0.135 mm thick latex diaphragm as selected from the banana model evaluation. The values for each of the data sets were consistent (see Figure 4.12). When evaluating the stress values of a specific material undergoing deformation it is essential to specify if the stress values are to expressed as engineering stress (σ_{eng}) or true stress (σ_{true}). With hyperplastic materials undergoing significant elastic deformation, true stress should be considered to account for changes in cross-sectional area.

The relationship of true stress to engineering stress for both uniaxial and equi-biaxial tension [112] can be expressed as:

$$\sigma_{true} / \sigma_{eng} = \lambda \tag{1}$$

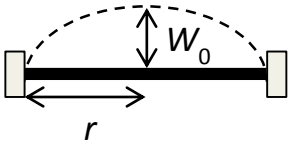
where λ is the stretch ratio in the direction of the applied load and is expressed as the ratio between the current length l and the initial length of the polar zone l_0:

$$\lambda = \frac{l}{l_0} \tag{2}$$

Engineering stress for the bubble inflation case is a function of pressure *P*, radius of curvature r_c, original thickness t_0 and stretch ratio λ [112], [114]:

$$\sigma_{eng} = \frac{Pr_c}{2t_0} \cdot \lambda \tag{3}$$

Assuming the membrane is flat in unstrained state (follows membrane theory of plates (flexural rigidity is negligible)), then the equation of maximum displacement at centre of a clamped circular membrane is given by (4):



$$w_o = k_1 * r * \sqrt[3]{\frac{P*r}{E*t}} \tag{4}$$

Where w_o is the central displacement, r is the radius, *P* is the pressure, *E* is Young's Modulus, *t* is the thickness, and k_1 is a constant.

4.3.2. Bench Top Results

Camera footage analysis generated the real-time inflation pressure *P* and corresponding bubble height. The parameters r_c and *l* were determined by arc-fitting to the bubble's radius of curvature using AutoCad software (Autodesk Inc, San Rafael, CA). The polar surface of the bubble was marked to indicate the elongation of the arc length as the bubble expanded. Figure 4.12 compiles the resulting values of the bench top evaluation with a polynomial trend line fitted to the plotted pressures.

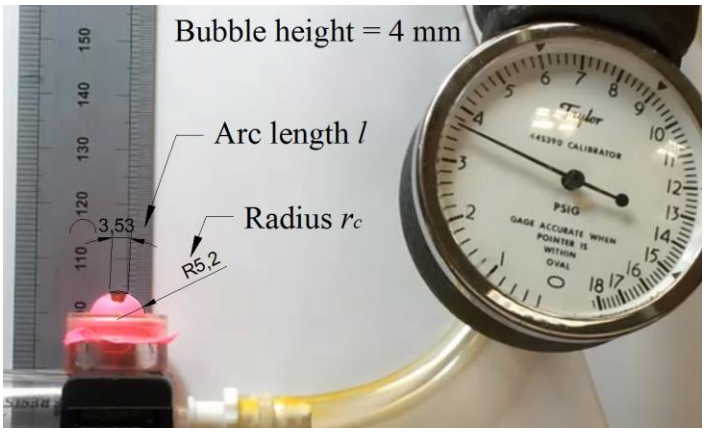


Figure 4.11 Graphic determination of the arc length *l* and radius of curvature r_c at a bubble height of 4 mm and corresponding inflation pressure of 25.51 kPa (3.7 psi).

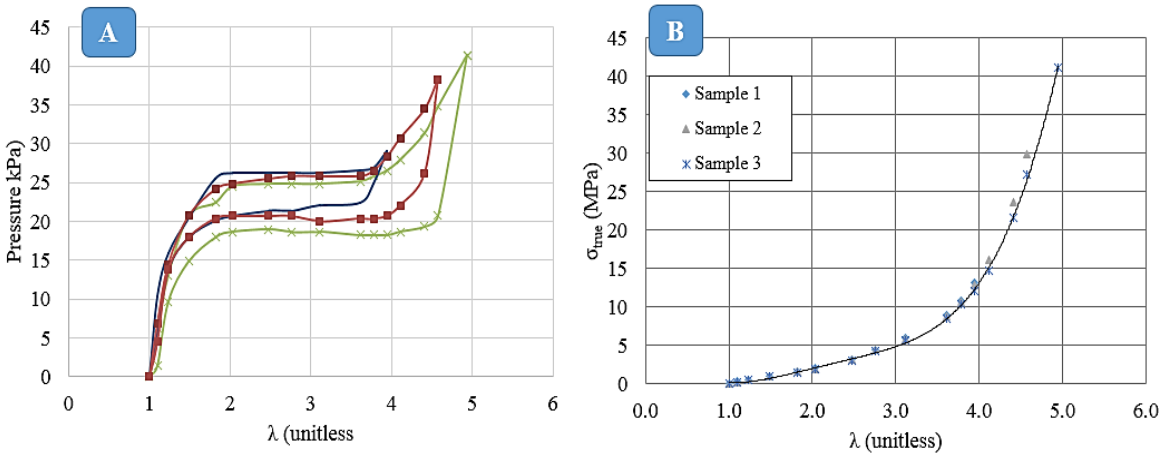


Figure 4.12 A) inflation/deflation cycle pressures and elongation ratio relationships for a latex membrane, and B) true stress and the stretch ratio with a fitted polynomial trend line during bi-axial bubble inflation testing

The elastomer initially demonstrates quasi-linear behaviour for small elongations ($\lambda \leq$ 1.8). The material then begins to yield as it quickly expands at almost constant pressure. The final domain of large deformation ($\lambda \geq 3.8$) sees the material undergoing strain hardening. The prototype remains within the elastic region for pressures up to approximately 25 kPa and elongations of 380%. Based on the findings of Tran *et al.* [86], the membrane would reach the domain of large deformations ($P \approx 37$ kPa, $\lambda \approx 4.7$) when passing through the ligamentum flavum. However this falls short of the burst pressure which was experimentally measured as 62 kPa at an elongation of approximately 960%. Figure 4.12 also illustrates the relationship between the true stress and the stretch ratio for three samples of a least square fit of thin latex diaphragm ($t_0 = 0.135$ mm). Again for the latex material tested, a linear plastic relationship exists up until an elongation ratio of approximately 380%.

Despite proving to be a very compliant and effective material during the early prototype evaluations, latex contains proteins and chemical allergens which may make it unsuitable as a material for medical devices. Natural rubber latex can be classified as a USP (United States Pharmacopeia) Class VI plastic, which certifies that the material is biocompatible and meets the requirements for leachates. However, more and more the market seems to be moving away from natural rubber as a result of concerns over possible adverse effects of Latex. Therefore an investigation into alternatives with similar characteristics to latex (i.e., high tensile strength, low elastic modulus and elongation at break > 600%) was required.

4.3.3. UMass Lowell Design Collaboration

The ProDural project was entered into the Massachusetts Medical Device Development Centre (M2D2) New Ventures Competition, Lowell, MA, USA in 2014. ProDural finished as one of four medical device winners from 15 finalists, who presented to a panel of distinguished judges from Smith & Nephew, UMass and Mass MEDIC. This included entrants from Europe, South Africa and North America. The prize awarded $5,000 worth of consultation from Smith & Nephew and UMASS Lowell which was used to carry out further device development as well as health economic analysis which will be discussed in later sections of this chapter.

As a result of the M2D2 New Venture competition, the author collaborated with Professor Stephen McCarthy and the plastics engineering team at University of Massachusetts Lowell to develop a highly compliant, biomedical grade diaphragm to replace the latex. Preliminary analysis compared the theoretical and actual behaviour of latex, silicone rubber, urethane rubber and liquid silicone (Dow Corning®). Table 4.5 provides an overview of the estimated principal mechanical properties of each of the examined materials. Following early assessment, the liquid silicone rubber Dow Corning® C6-530 Class VI elastomer was selected based on its high tear strength (27.5kN/m), tensile strength (8.2 MPa), elongation (831%) and its reported use as a medical grade elastomer.

Table 4.5 Mechanical properties of examined material (www.matbase.com).

Material	Natural Rubber	Silicone Rubber	Urethane Rubber	Dow Corning® (C6-530)
Est. Tensile Strength	20-30 Mpa	5-8 Mpa	20-30 Mpa	8.2 Mpa
Est. Elongation at Break	750-850%	200-800%	300-450%	831%

The Dow Corning C6-530 samples were formed using compression moulding. The two part process was mixed by hand while adding a blue pigmentation and then de-aired in a 700 mmHg vacuum for 1 hour. The resulting mixture was spread evenly onto aluminium plates separated using brass shims. The plates were then pressed together at 300MPa and 120˚C for 5 minutes. A 12.5 mm circular punch tool was used to extract membranes from the resulting sheet of Dow Corning.

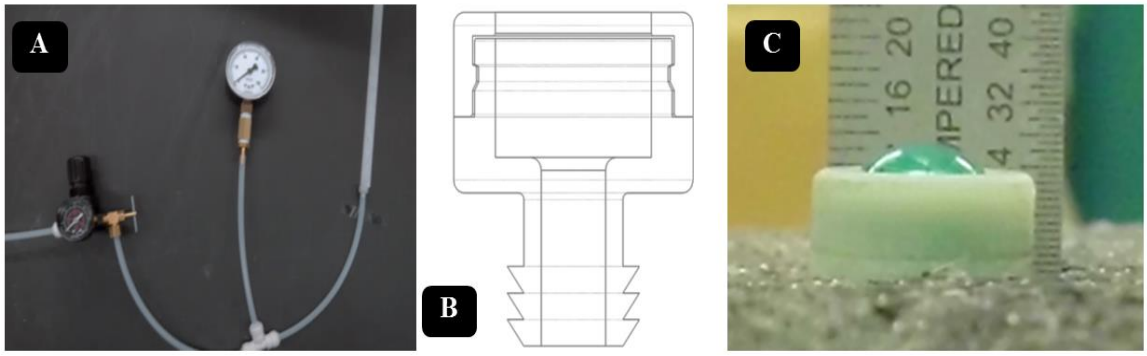


Figure 4.13 Pressure test setup with A) test setup with low pressure air regulator, B) CAD assembly drawing adapted from ProDural dimensions, and C) 3D printed prototype.

This process was repeated to produce a number of sheets of varying thickness of between 76 – 203 µm. The samples were subsequently assembled in an Objet Eden 3D printer model produced with VeroWhite photo-cured material, and connected to a low pressure air regulator which was monitored with a precision gauge. The resulting displacements and inflation pressures were captured and graphically analysed using ImageJ software (see Figure 4.13).

The diaphragm constraints were determined due to the geometrical restrictions of standard 7ml LOR syringes. As detailed in Appendix 5, an aperture with a diameter of 7.5 mm may be created using a snap fit cap design with an overall outer diameter of 11mm. This provides sufficient wall thickness to create the overlap required for the snap fit connection. Based on end-user feedback, the desired inflation pressure to create an inflated diaphragm (i.e., bubble height ≥ aperture diameter/2) was estimated at 20kPa. The burst pressure was rated at 60kPa which provides a factor of safety of 1.5 of the maximum pressure recorded by Tran *et. al.* (2009) [86]. The resulting pressure and corresponding displacement curves are plotted in Figure 4.15. Each of the samples demonstrated a quasi-linear behaviour with sudden rupture on reaching maximum burst pressure rating.

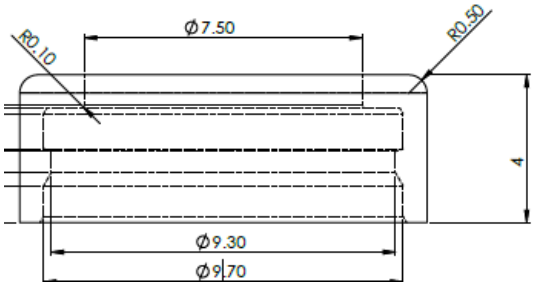


Figure 4.14 Selected detail of diaphragm cap (see Appendix 5).

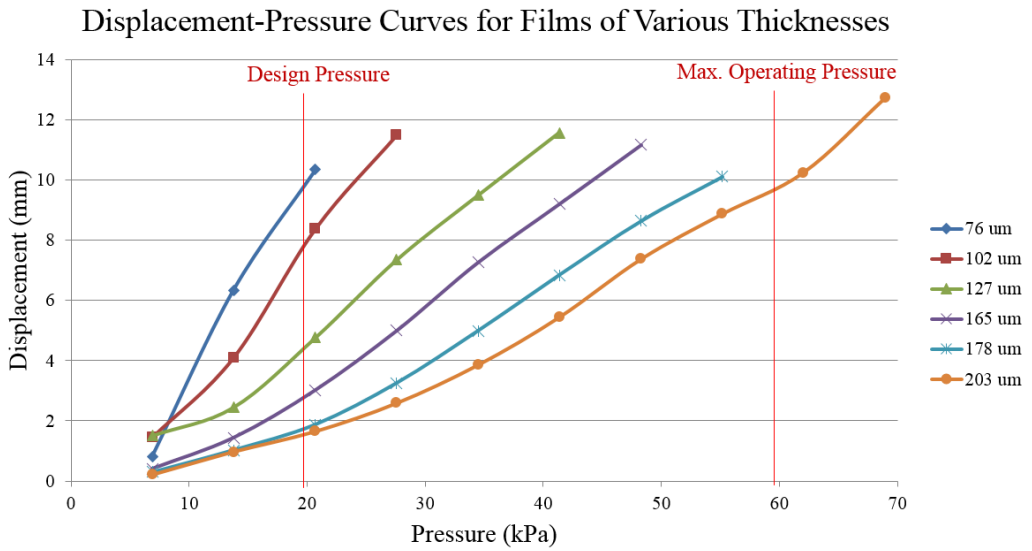


Figure 4.15 Results from pressure testing with varying sample thickness.

Figure 4.16 provides a more detailed look at the resulting displacements at the desired operational inflation pressure of around 20kPa.

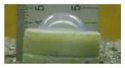
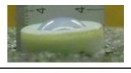
Film Thickness	Image @ 20.7kPa	Displacement @ 20.7kPa
76 um		10.3 mm
102um		8.4 mm
127um		4.8 mm
165um		3.0 mm
178um		1.9 mm
203um		1.7 mm

Figure 4.16 Displacement at 20.7kPa for liquid silicone of varying film thicknesses (source UMass Lowell).

The C6-530 silicone rubber has great balance of tear strength and elasticity. A film thickness of between 6.5 mil (165 µm) and 5 mil (127 µm) meets the operational performance constraints. However, thicknesses with vertical displacements greater than the aperture radius at 20kPa ruptured at pressures lower than 60kPa. The thickness can be further fine-tuned to allow large displacements and high rupture pressures. A film thickness of 8 mil (203 µm) was recommended since it will not rupture at 60kPa, which is within the margin of error for maximum operating pressure presented by Tran et al [86].

4.3.4. Failure Mode Analysis

A DFMEA of the ProDural device was produced as part of the design control process (see Appendix 4). The only additional risk, when compared with standard LOR syringes, relates to the visual indicator. The indicator may fail either by leakage at the cap or over-inflation of the membrane causing rupture. The clinical impact in either case is minor, resulting in a failed attempt to identify the epidural space, requiring a replacement device. Other risks such as over advancement of the needle beyond the epidural space is common with the existing method. All identified risks are reduced so far as possible to acceptable levels in terms of probability of occurrence and severity to the patient. Acceptable risk levels are described in the risk management standard operating procedure (SOP 7.1). Risk mitigation methods include risk reduction through inherent safety in design, risk reduction by protective measures in the manufacturing process, and risk reduction through the supply of information for safety.

4.4. Pre-Clinical Investigation

A pre-clinical human cadaver study was completed by a consultant anaesthetist, Dr Peter Lee, at the University College Cork FLAME laboratory. The primary objective of the study was the technical feasibility of ProDural in locating the epidural space with both air and water as an inflation medium. The secondary objective was to compare ProDural to existing technologies for (1) amount of fluid injected on reaching the epidural space, (2) ease of use, (3) effectiveness in finding the epidural space, and (4) length of needle insertion. Finally a number of different ProDural prototypes were used varying in diaphragm material and thickness and aperture diameter to determine optimum characteristics based on end user feedback.

Several repeated tests were executed to establish the effectiveness of ProDural at identifying the epidural space in a freshly preserved cadaver. The unembalmed cadaver used in this investigation was that of a 99 year old female. The cadaver was in excellent condition, frozen within 24 hours and thawed 48 hours before the investigation, and the vertebral column was intact from the cervical to T11 vertebrae. The spine demonstrated scoliosis consistent with cadaver age. The cadaver was placed in the supine position with a slight right tilt. Using the conventional LOR technique and an 8ml Perifix syringe (B.Braun), the clinical investigator introduced a needle tip into the subarachnoid space in the region of T5. Once the subarachnoid space was located, a catheter was inserted and

methylene blue dye was infused into the subarachnoid space. This approach facilitated investigation of dura puncture where blue dye would become visible on aspiration.

4.4.1. Epidural Administration with Air as the Inflation Medium

The first assessment was to compare ProDural with conventional LOR syringes (8 ml Perifix and 7 ml Epilor syringe) using air as the inflation medium. The conventional LOR syringe was firstly used to identify the epidural space at T9. Using the midline approach and a pulsing LOR technique, the clinician identified the epidural space. The needle depth (4.8 mm) and the volume of air injected (2.5 ml) were recorded. The syringe was then removed and the needle site was aspirated. Blue dye did not become visible on aspiration, therefore it was concluded that the dura had not been punctured. The needle was then removed. The test was repeated in the same region using a ProDural syringe. ProDural was advanced using the midline approach as before until an apparent collapse of the visual indicator was observed (see Figure 4.17). The position of the needle was marked as point 1 (P1) and both the needle depth (4.6 mm) and injected volume (1 ml) were measured. Subsequent aspiration failed to identify blue dye. The ProDural syringe was removed and the needle was left in place. Succeeding dissection would demonstrate whether or not the needle at this point punctured the dura.

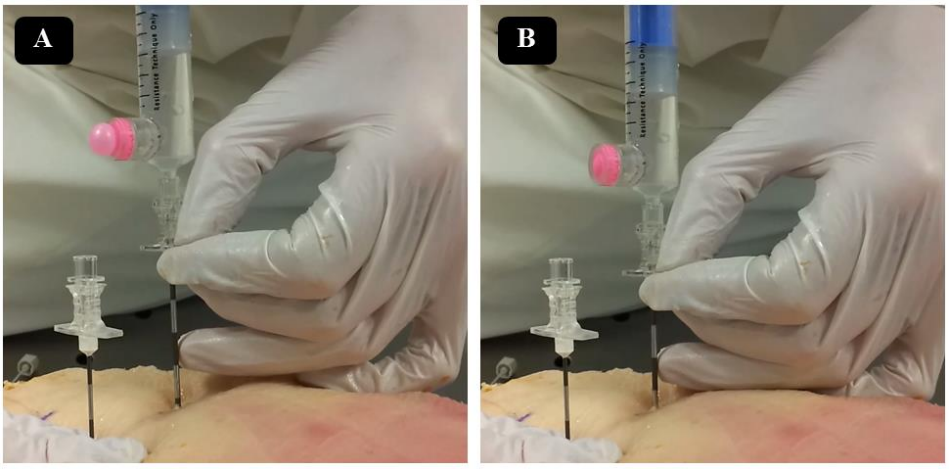


Figure 4.17 ProDural prototype used in pre-clinical cadaveric trial in A) its inflated state advancing towards the epidural space, and B) its deflated state on needle tip entry into the epidural space.

It was noted that there was no apparent negative effect using ProDural over the commercial LOR syringe in terms of ease of use. The instant collapse of the

diaphragm resulted in less air being inserted into the epidural space and allowed the clinician to maintain the LOR technique. The pink visual indicator was easily apparent and preferred over the more neutral white diaphragm.

4.4.2. Epidural Administration with Water as the Inflation Medium

The next assessment was to establish whether or not there was a perceivable difference using water as the inflation medium. The insertion region for this test was T10. The 7 ml Epilor syringe by BD was used for the conventional syringe as the graduations on the barrel were more defined. The barrel was charged with 5 ml of water and the syringe and needle were advanced until a loss of resistance was perceived whereupon the syringe had discharged to 3 ml (2 ml injected). The needle length measured approximately 4.5 mm. Aspiration ruled out dura puncture, and the needle was removed.

ProDural was also charged with 5ml of water and advanced until the bulging diaphragm collapsed. The resulting needle length measured approximately 5mm and the volume of fluid injected measured approximately 1 ml. The ProDural syringe was removed and the needle left in place. The point was marked as P2.

The ease of use and effectiveness was comparable to the existing LOR syringe with no perceivable drawbacks. The near instant collapse of the visual indicator reduced the user's reaction time, thus reducing plunger advancement. There was no apparent disadvantage in using water over air.

Figure 4.18 Cadaver assessment of a 10ml ProDural prototype.

4.4.3. Aperture Diameter Impact Assessment

The next assessment reviewed prototypes of varying aperture diameters on device performance and usability. The three sizes assessed were 6.6 mm, 7.5 mm and 10 mm (site marked P3). There was no perceivable difference in the ease of use between the larger and smaller prototypes. The larger diameter required less pressure to displace the diaphragm outwards and its percentage elongation is not as extreme (see Figure 4.18). In addition the larger inflated surface further emphasised the loss of resistance when detected. However, the smaller prototype may look neater and less cumbersome at little or no cost in performance. The decision on final device geometry may therefore depend on appearance and ergonomics.

4.4.4. EpiDrum Comparison

The final test compared the Epidrum device to ProDural. An Epidrum device (see Figure 4.19) was charged and advanced with an epidural needle towards the epidural space in the region of T6. Despite several attempts the Epidrum bulge failed to collapse. The pressure required to inflate Epidrum was far less than that of ProDural and thus may have led to tissue lodging and blocking the advancing needle.

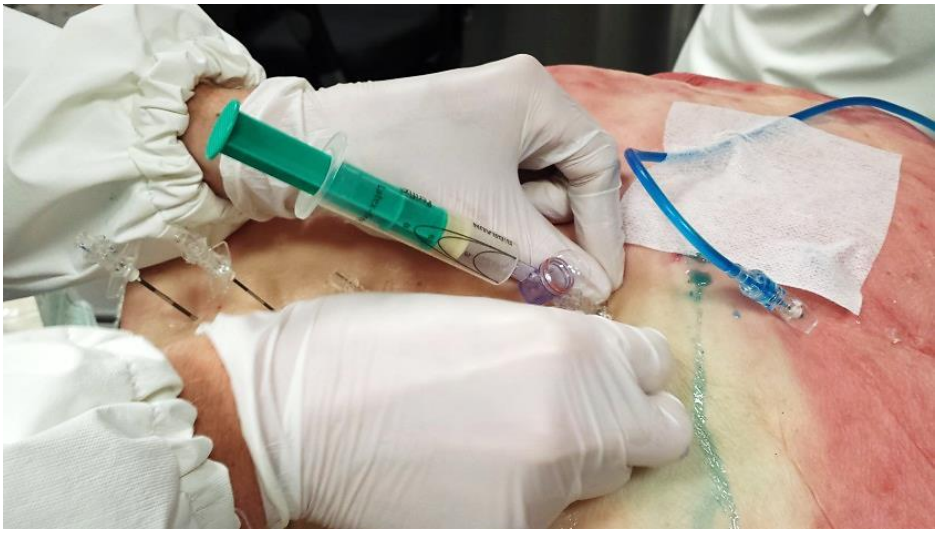


Figure 4.19 Epidrum epidural location device in use as it is advanced towards the epidural space.

The 10 mm diameter, pink latex ProDural device was then used in the same location. At this point, the area was becoming compromised due to the number of insertion attempts with Epidrum, thus the visual indicator in ProDural would begin to leak as soon as it was charged and it was nearly impossible to further locate the epidural space in this region.

The 10 mm prototype then moved to the cervical region between C6-C7 and reapplied. The smaller 6.6mm diameter ProDural with a 0.13 mm thick latex membrane and a further ProDural with a 0.18 mm thick latex membrane were subsequently used until the epidural space was located (point P4). The thicker 0.18 mm prototype, which was charged with air, displayed a very evident loss of resistance on reaching the epidural space. It was noted that the initial pressure to form a defined bulge was greater in the 0.18 mm thick prototype.

Additional sites were selected to further compare Epidrum with ProDural. However all subsequent attempts failed to locate the epidural space. The vertebral column was no longer sufficiently intact to carry out further tests.

4.4.5. Pre-Clinical Dissection

The investigation concluded with a dissection in order to demonstrate that the epidural space had been reached and that the dura was not punctured (see Figure 4.20). An anatomist dissected the region in a layer-by-layer fashion and care was taken to expose the distal tip of the epidural needle without moving it from its position. The needle positioned at points P1 and P2 were first to be examined. After careful dissection it became clear that at these locations, ProDural successfully located the epidural space without puncturing the dura. The dissection continued to expose points P3 and P4. It was noted that the needle tip in each case was located in the epidural space without underlying dural puncture.

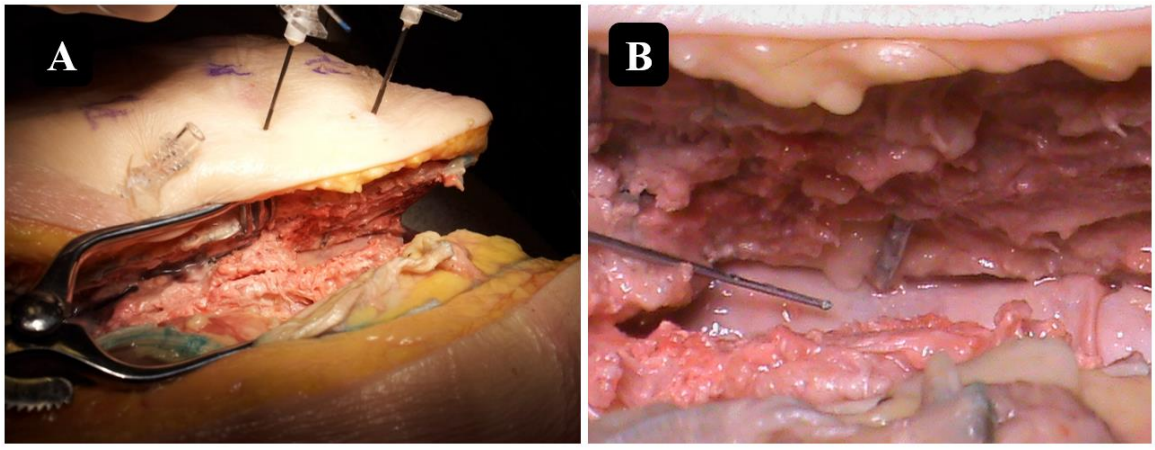


Figure 4.20 A) posterior dissection to reveal tip of ProDural placed epidural needles, and B) close up view of needle tip location P1 illustrating that the dura was not damaged and the needle tip was successful placed in the epidural space.

4.4.6. Pre-Clinical Conclusions

ProDural was found to be at least as effective and easy to use as a conventional LOR syringe. In both the air and water tests, ProDural introduced less fluid on detection of loss of resistance (65% reduction) and was subsequently proven to have reached the epidural space without puncturing the dura by means of exposing the needle tip through dissection. The immediate collapse of the visual indicator improved the reaction time of the user preventing excessive advancement of the plunger and epidural needle. Clinical feedback cited a bright colour (e.g., green or yellow) as preferable for the diaphragm. In most cases, the epidural is administered in a dark labour ward in the middle of the night, and bright colours would aid in the detection compared to more neutral colours. It was found that thinner membranes performed better due to the smoother transition from the elastic to plastic states. The diameter of the diaphragm played little role in performance and may be refined to look most appealing to the end user. There were several shortcomings in the investigation. The model used was not optimum due to the age and absence of the lumbar region. As the investigation progressed, it proved increasingly difficult to determine the epidural space. Due to the degrading effect of repeatedly introducing needles, it was not possible to carry out several repeat tests along the vertebral column. Notwithstanding these limitations, the study indicated that ProDural represents a very promising device for identifying the epidural space. Furthermore, the success rate in identifying the epidural space indicates an effective design solution. More studies are necessary to determine if ProDural can effectively reduce rates of accidental dural puncture or 'false positive' rates. The results of the bench-top trials and pre-clinical investigations were presented at IASTED International Conference on Biomedical Engineering, Zurich (2014) the proceedings of which were subsequently published [9].

4.5. Commercial Feasibility

A second objective of the epidural project was to assess the commercial feasibility of the resulting device with the aim of exploring business opportunities. The ProDural project was successful in applying for a clinical innovation award (2013), sponsored by Enterprise Ireland and supported by the Cleveland Clinic Ohio. This award was leveraged to evaluate the commercial feasibility of the proposed device as well as accommodating meaningful engagement with clinicians at the Cleveland Clinic to evaluate clinical utility. In addition, the M2D2 New Ventures award previously

described, was used to produce a health economics report in collaboration with Smith & Nephew (Smith & Nephew Inc., Andover, MA). The following section will describe the results of commercial feasibility assessment.

4.5.1. Epidural Market Assessment

The European market for regional anaesthesia was estimated at $14.8 million in 2011 with projected growth to $30.7 million by 2018. A Frost and Sullivan report (M7C3-54, 2011) listed an average epidural tray cost of $15 (estimated syringe cost is $2-$4) with strong market growth. Key market growth drivers include emerging market epidural uptake especially in obstetrics, increasing incidences of therapeutic epidurals, and continuing increases in general surgery volumes due to obesity.

The US Department of Health and Human Services indicate that based on information provided by a total of 36 reporting states and the District of Columbia, in 2011 out of 3.267 million live births, approximately 2.3 million or 70.85% involved the application of epidural or spinal anaesthesia during labour. This rate was higher for Whites (74.6%) compared to Blacks (7.32%) and Hispanic (61.6%) and, as a general rule, the level of treatment with epidural or spinal anaesthesia declined with the advancing age of the mother. Given that the total number of live births in the US was 3.99 million in 2015, applying the 2011 epidural rate suggests that approximately 2.82 million deliveries in 2015 involved the provision of epidural/spinal anaesthesia during labour (see Table 4.6).

Separate to labour applications, there are also over 8.9 million therapeutic epidurals performed in the U.S. each year [115]. Based on the current incidence rates of accidental dural puncture (approx. 1.5% [87]), this equates to approximately 175,000 clinical events costing the US healthcare system an estimated $330 million dollars per year (based on an inpatient day cost of $1,878/day [116]).

Table 4.6. Global Epidural Market 2013.

Market	Annual births	Neuraxial block rate	Epidural or spinal blocks in obstetrics	Therapeutic epidurals	Total epidural market
Ireland	74,000	37%	27,380	5335	32,715
UK	729,674	33%	243,225	74,000	317,225
USA	3,900,000	71%	2,763,150	8,900,000	11,663,150
EU28	4,396,326	33%	1,465,442	586,219	2,051,661
Total	**4,214,000**		**4,499,197**	**9,565,554**	**14,064,750**

EU27 is UK-correlated and does not include ROI/UK

The typical Medicare reimbursement for an epidural shot is $200 if given in a doctor's office, $400 if done at a surgery centre and about $600 if performed at a hospital [115]. Between 1994 and 2001, use of epidural injections increased by 271% and facet joint injections by 231% among Medicare beneficiaries [117]. Total inflation-adjusted reimbursed costs (based on professional fees only) increased from $24 million to over $175 million over this time period. More recent data indicate continued rapid growth in use of spinal injection therapies among Medicare beneficiaries, with an increase of 187% in use between 2000 and 2008.

The scope of application outside of anaesthesia is vast. Numerous clinical indications were assessed by clinical engagement (e.g., PEG tube placement, trauma settings, abscess and urinary drainage etc.). Trocar placement was identified as high-potential due to (1) clear unmet clinical need, (2) large volumes, and (3) clear go-to-market strategy leveraging existing relationships with clinical champions.

ProDural may find use in both closed and direct trocar insertion techniques representing a global market opportunity of over 10.7 million annual laparoscopic procedures (see Section 3.5.1). By replacing high-cost Veress needles (US $22-45) with a low-cost device, a commercially viable proposition may be possible.

4.5.2. Key Opinion Leader's Feedback

With the support Enterprise Ireland, two of the promoters (Dr Peter Lee and Conor O'Shea) travelled to Cleveland Clinic (Nov 2013) where a clinical focus group was conducted with a number of Cleveland anaesthetists. The key outcomes from the focus group are as follows:

- As much as one dural puncture occurs per week within the training programme in Cleveland (i.e., 1/30-40 procedures per week).
- Approximately one in every 20-25 procedures would result in a spinal tap, with a blood patch typically required once per month.
- It would be difficult to prove that a device can reduce the already low incidence of spinal taps as this is quite small number and may not sway the purchasing bodies.
- It may be more useful to demonstrate a reduction in the number of false positive administrations particularly in obese patients as this is a more significant problem.
- When compared to the Epidrum and Episure devices, ProDural was preferred for usability amongst the clinicians.

- The fact that ProDural allowed clinicians to continue LOR with air or water was rated positively.
- Conceptually and intellectually, the respondents were interested in ProDural's facility to provide a visual indicator that the epidural space had been reached.
- From a teaching point of view, having a visual indicator is very useful when confirming that a trainee has reached the epidural space.
- It was largely felt by this group of anaesthetists that a clinical trial would be required before adopting such a device but they were willing to test ProDural once available.

ProDural was also presented at a number of other Irish and US clinical centres (CUH, Mater Dublin, Harvard Medical School, Brigham and Women's hospital, Massachusetts General Hospital). In general, there was positive feedback from anaesthetists in both the US and Ireland as evidenced by their willingness to support clinical studies. However, the clinicians while expressing their interest in discovering new devices were also quick to point out that anaesthetists as a profession, particularly those working in maternity hospitals, tend to be conservative in their choice of techniques and tools. This frequently translated to a resistance to change.

As part of the M2D2 New Ventures Competition, a report was produced in collaboration with Smith & Nephew which summarised the results of three interviews with anaesthetists (a fellow in Pain Management, an Associate Professor of Anaesthesiology and a Professor of Anaesthesiology). The three respondents, whose identity remained anonymous, had varying levels of post-residency experience (years: 3, 22, 30). The key comments made were as follows:

- An additional safety measure is attractive. Education would be the major application for this device
- If the miss is a dural puncture, 50% of patients get a spinal headache, 50% are free of any symptoms. For those with a spinal headache, 50% need a clot to seal the hole. 50% respond to medication & hydration.
- Other uses for this technology (include) entering the abdominal cavity in laparoscopic surgery. Both the epidural space and the abdominal cavity are under slight negative pressure.

- Novel idea. Some people are better than others with haptic feedback. Hard to say whether this is based upon experience only. Those who don't do many epidurals per year may be more receptive to this technology.
- We need a better way to identify the epidural space than we currently do; it is very operator dependent. If used in teaching, it is possible this will be rapidly adopted.
- Concerns: Will the indicator add significant weight to the syringe? Is air entering the epidural cavity? ("An air bubble can prevent anesthetic from working. If it injects 0.5cc, it's ok; we can aspirate that. It would be unacceptable to inject 3cc of air").

In addition to engaging with the clinical community to assess the clinical utility of the presented device, ProDural received commercial validation in the form of securing a top four finish at the MedTech Idol (Innovator) Dublin 2014. Thirty-six early-stage medical devices entered the international contest and ProDural was among just four finalists to take the stage for the MedTech Idol competition organised by RCT Ventures at the Informa Investment in Innovation (IN3) Medical Device 360° Dublin conference.

4.5.3. Health Economics Analysis

As a further result of the work carried out with Smith & Nephew, a review of the addressable US market size based on CPT coding information, and a basic health economics assessment was also carried out. The Current Procedural Terminology (CPT) code describes medical, surgical, and diagnostic services and is designed to communicate uniform information about medical services and procedures among physicians, coders, patients, accreditation organizations, and payers for administrative, financial, and analytical purposes [118]. Using the Truven Health Analytics tool which reports information on billed CPT codes, data was analysed for 2011-2014 on a number of relevant procedures where an epidural needle placement is required. This information yielded the following observations:

1. The number of spinal/epidural placements annually in the US is at least 7 million per year, as reported by the Truven Health Analytics site.
2. The number of spinal/epidural placements annually in the US could be as high as 30 million, as back-calculated from the number of epidural blood patches, one of the treatments for post-dural puncture headaches, of which there are over 50,000 administered annually in the US.

In terms of health economics analysis, a paper by Dakka et al [119], was identified with a retrospective analysis of patients receiving dural punctures with a cutting needle, limited to a single centre. Costs associated with post-dural puncture headaches (PDPH) at Henry Ford Hospital in Detroit, Michigan were estimated, and then, using the actual rate of PDPH among patients and taking the literature-reported rates for PDPH following lumbar puncture, the theoretical cost savings that would have occurred, had atraumatic needles been used, were calculated. The theoretical cost savings were $45,435 for the 274 patients (or $166 per patient), assuming no difference in price between the two needles. Given that this figure corresponds to a theoretical elimination of 27 headaches, the costs per headache can be assumed to be $1,682 ($45,435/27 = $1,682 per patient additional cost burden resulting from a PDPH).

If the ProDural device is able to eliminate 4 out of 5 accidental lumbar punctures, in experienced hands, this will reduce the PDPH from 2.5/1,000 to 0.5/1,000 (assumes a half of accidental punctures result in PDPH). If the PDPH costs are taken from the Dakka paper, this reduction in PDPH will realise a cost savings of 2 × $1,682 = $3,364 for 1,000 patients, or $3.36 per patient.

Taking the $3.36 per patient cost savings and using a 11.72 million figure for epidurals in the US (8.9 + 2.82 million), and assuming no price differential between ProDural's syringe and existing syringes, the total benefit to the healthcare system would be 11.72 million × $3.36 = $39.42 million if all epidural syringes were converted to ProDural technology. In theory, ProDural could charge an extra dollar over the existing syringes and the cost savings to the payers would still collectively be $27.7million (11.72 million × $2.36).

4.5.4. Intellectual Property Prior Art Review

A European provisional patent (EP14150806) was filed as part of this PhD research project for the presented invention entitled "An indication device and method for locating a natural cavity in a body" in January 2014. The provisional patent application identified the key novel and non-obvious features of the device compared to prior art. The principal comparable devices are those that use the differential pressure method to indicate entry into the epidural space. The two closest competing patents identified were US 7,175,608 (Epidrum) [99] and US 5,902,273 (Yang and Yang, not commercialised) [120].

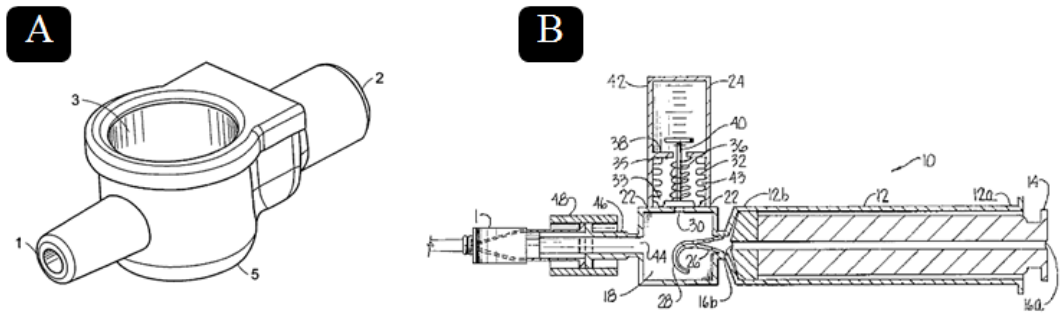


Figure 4.21 A) US patent number 7,175,608 (Epidrum), and B) US patent number 5,902,273 (Yang and Yang).

The key distinguishing, novel and non-obvious features of ProDural which are not evident from review of the identified prior art were:

- An all-in-one syringe including diaphragm membrane construction,
- Maintenance of the LOR technique on epidural entry,
- Visual indication by means of a deflating diaphragm integrated within the syringe body.

In addition, the present device has the potential to provide visual indication of entry into any natural body cavity which is subject to transcutaneous needle puncture. Clinical settings where this is relevant include but are not limited to:

- Identification of the peritoneal cavity during laparoscopic surgery
- Percutaneous endoscopic gastrostomy (PEG) tube placement
- Percutaneous suprapubic catheterisation for bladder drainage
- Percutaneous abscess drainage

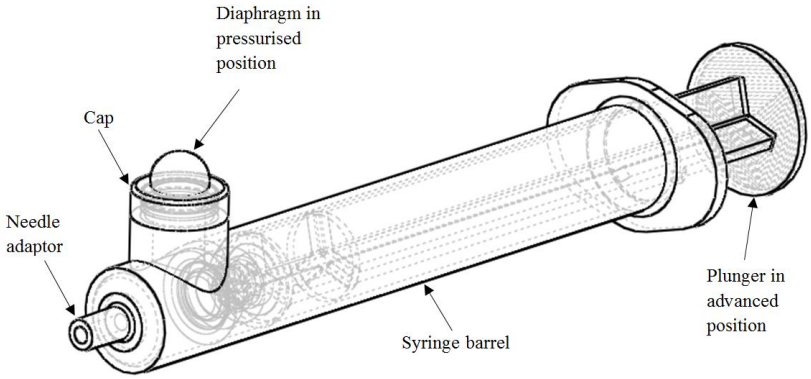


Figure 4.22 ProDural design with visual pressure drop indicator integrated into the distal end of the syringe barrel.

Subsequent to the provisional patent filing, a European Search Report identified a potentially infringing patent filed on the 24th February 2010 in China. CN201409922

(Dong Sun) discloses a syringe device whereby one embodiment (Figure 4.23) of the invention includes a visual indicator on the syringe barrel comprising an elastomer. However this device operates on a different principle to that of the present invention. CN201409922 does not maintain the loss of resistance technique upon entry into the epidural space. In this disclosure, the plunger is rotated into place rather than pushed. This differs significantly from the ProDural embodiment and does not make the embodiment of '922 compatibly with maintaining loss of resistance on epidural entry.

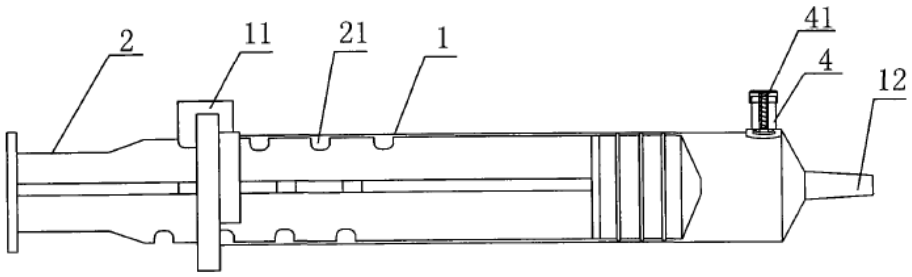


Figure 4.23 Potentially infringing patent (CN201409922) discovered during European search report.

In addition, '922 discloses an elastomeric member (41) connected to the pedestal of the indication column via a spring which under increased intra-barrel pressure, stretches upwards. As the plunger is rotated via a slotted configuration and increases pressure within the barrel, it excites the membrane causing it to extend outward. At this point, LOR is no longer used and the complete syringe and needle assembly are advanced by pushing the system toward the epidural space until such time as a pressure drop at the needle tip is detected causing the spring to collapse the membrane. This embodiment is significantly different to the ProDural proposition.

Despite clear differences in construction and deployment of ProDural and CN201409922, the overall claims disclosing a visual indicator incorporated into a syringe barrel to signal epidural entry presented an issue for the ProDural project. Limitations of resources for both time and finances prevented further exploration of the IP to investigate other areas of novelty to secure clean protection. To the knowledge of the team, patent '922 and its inventor Dong Sun never proceeded to commercialise this filing which presents opportunities for future IP acquisition or indeed licencing. The clear differences in design and method of use also presents an opportunity for further device development to overcome concerns of inventiveness and to proceed with successful patent filings.

4.5.5. Device Regulatory Classification

The regulatory classification of the presented device follows the rules listed in Annex IX of Directive 93/42/EEC as amended, and schedule 9 of related Irish regulation (S.I. No. 252/1994). ProDural falls within the scope of the directive as a medical device, as defined in Article 1 of Directive 93/42/EEC and Article 2 of the national Regulation.

This device will be designated as a standalone device, with an intended use of signalling correct location or entry of a probe such as an epidural needle or the like into a natural cavity in a body through both visual and tactile feedback for a continues use less than 60 minutes (transient) and is non-invasive. Therefore according to rule 2 of 93/42/EEC Annex IX, ProDural may be classified as a Class I device.

Furthermore, ProDural may be classified as a Class 2 device under FDA recognized consensus standards, specifically related to regulation number 880.5860 and product code FMF which is concerned with the device name “syringe piston”.

4.6. Chapter Review

The goal of this work was to design and develop a medical device which can advance the efficacy of epidural administration with a potential alternative application of peritoneal cavity detection in laparoscopic surgery. With over 2.8 million patients receiving epidural or spinal anaesthesia during labour in the US alone, it is of paramount importance to identify a more reliable method of epidural administration. The proposed solution maintains the popular tactile feedback associated with the LOR technique whilst potentially enhancing operational performance through an integrated visual pressure drop detector.

4.6.1. Technical and Commercial Review

The instantaneous collapse of the diaphragm may improve the clinician’s reaction time thus preventing excessive needle advancement and reducing the risk of accidental dural puncture. ProDural may also reduce the risk of false positive readings in obese patients as the clinician may vary the applied pressure to determine when the epidural space has been reached. The contrasting bright surface of the diaphragm ensures clear visibility even in a dimly lit maternity ward. Finally, ProDural may reduce the steep learning curve associated with epidural administration as the bulging

diaphragm allows teaching clinicians to visually determine correct placement by their trainee doctors.

The final development of a fully specified ProDural device to design freeze was hampered due to financial and time limitations. However, the solution proposed in this work does point to a promising and effective method of identifying the epidural space. Further design verification is required to prove that the current snap fit design is sufficient to prevent any leakage from the inflated diaphragm. In addition, further work is required to finalise a material which is biocompatible and meets all the design specifications. Finally, additional resources are required to get further opinions on patentability and to explore additional novel functionality.

While the results of this preliminary analysis and experimentation are encouraging, a clinical investigation will be required to investigate whether or not ProDural can statistically reduce the incidence rate of accidental dural puncture and for false positive readings. The size and cost of a future clinical study which would be sufficiently powered to show the efficacy of ProDural at improving patient safety, has yet to be determined. The mechanical experiments defined the relationships between the inflation pressure and true stress and stretch ratio for the current device configuration. The pre-clinical study served as a technical feasibility evaluation verifying the proof of concept and suggested that ProDural is at least as effective and easy to use as existing LOR syringes. The most significant advancement noted in the study is the improved reaction time on reaching the epidural space. This may reduce the risk of accidental dural puncture and consequently reduce costs to the healthcare provider due to shorter hospital stays. It was also demonstrated that ProDural introduced less volume of injection fluid that would otherwise dilute subsequent anaesthesia and may cause air embolisms and or other complications [83], [121].

Future work is required before ProDural may be evaluated in a live human investigation. The operational nature of ProDural is one that requires a smooth transition from the original undisturbed diaphragm position to the inflated state ($\lambda \approx 4$). The highly elastic nature of natural rubber latex with an elastic modulus of between 1 and 5 MPa was ideal for the early technical evaluation of ProDural. Collaborative work with UMass Lowell analysed the physical and mechanical characteristics of a medical grade silicone rubber. However questions still exist relating to the performance of this material. From a

commercial point of view, ProDural has a potential of fulfilling a gap in a quickly expanding market with meaningful cost benefit from a health care providers point of view. The current results point to a promising alternative epidural space location device which has the potential to help alleviate complications and cost in epidural administration.

4.6.2. Design Control Review

Similar to the laparoscopic retractor project described in Chapter 3, the epidural project began before the design control process was implemented. However, as with SecuRetract, all commercial research and design development activities were recorded and used to populate the Design History File. Currently ProDural is in Phase III of the design and development process as described in Chapter 2. As qualitatively illustrated in Table 4.7, the ProDural project has only began to progress through the Phase III activities. Despite independently classifying each of the five phases of design development, certain activities have progressed beyond the phase boundary. As a result of the Enterprise Ireland Clinical Innovation Award and the M2D2 New Venture Award, particular emphasis has been placed on the commercial opportunity and market launch strategy, which exceeds what is typical of the earlier phases.

At times during the implementation of design controls, the documentation seemed burdensome; having to document the justifications for design iterations, populate the DDP and DFMEA and record interactions with the end-users. However, on reflection, these records served to command project focus and achieve target milestones as well as proving detailed historic evidence of developmental activities. Due to the inherent simple nature of ProDural in terms of design, retrospective population of the DHF may be achieved quite easily. However additional time and resources are required to fully populate the DHF to ensure compliance with the requirements of the design control process. The main drawback from retrospectively applying a controlled design process to a project is that certain activities, such as planning for design for manufacture, occur later on whereas earlier consideration may have led to different material selection at an earlier phase.

The ProDural project provides a case study of what typically occurs when a seemingly novel solution comes against potential intellectual property infringements. Despite presenting an exciting proposal to and end-user identified need to a global

problem, the ProDural project struggled to get the financial aid to support more extensive development activities. In the corporate world, entities have additional resources to pursue formal opinions of patentability and/or focus on specific functionality or aspects of the design whereby claims may be secured. Alternatively, the option of acquiring/licencing the patent in question would be pursued should the project align with corporate strategy. However, in the case of university projects which typically rely on government and/or departmental finances to support product development, the prospect of infringing claims can be a detrimental factor to securing aid. Despite this, the ProDural may still serve as an exemplar to the introduction and administration of the design control process developed as part of this work.

Table 4.7 ProDural project progression.

Phase Activity Completion	Phase I	Phase II	Phase III	Phase IV	Phase V
	Clinical Need Definition	Design and Development Plan	Detailed Requirements Specifications	Design Transfer / Pilot Production	limited Market Release
	100%	100%	20%	0%	0%
	Concept Solutions / Early Risk Assessment	Define Design Inputs	Manufactures / Suppliers Identified	Final Design Validation	Post-Market Surveillance
	100%	100%	20%	0%	0%
	Early Commercial / Market Assessment	Initiate Quality Documentation	Risk Assessment Update / Implement Risk Controls	Complete DHF, DMR, Technical File	Sales and Physician Training
	100%	75%	20%	10%	0%
	Early Intellectual Property Review	Build and Evaluate Prototypes	Verification & Validation Protocols	Artwork / Traceability	Expand Sales Effort
	100%	100%	0%	20%	0%
	Early Regulatory Assessment	Expanded IP landscape Review	Build Units for V&V	Market Launch Strategy	Continuous Improvement
	100%	100%	0%	20%	0%
		Risk Analysis Update	Process Validation Plan	Manufacturing Qualification	Quality Audits
		100%	0%	0%	0%
		Define Regulatory Requirements	Confirm Intellectual status	Regulatory Approval	
		100%	20%	0%	
		Business Plan	Update DHF / Business Plan	Build Inventory / Scale Up	
		25%	20%	0%	

Chapter 5 SafeTrac: Safer Tracheal Intubation

Tracheal intubation, often simply referred to as intubation, is a medical procedure that involves the placement of a flexible plastic tube into the trachea (windpipe) to preserve an open airway or to serve as a conduit through which to administer certain drugs. Despite tens of millions of these procedures being performed annually worldwide, airway intubation remains one of the most difficult anaesthesia activities. This project aimed to develop a low cost disposable device to improve the ease of intubation, particularly in cases of difficult intubation. Unlike previously described devices in this thesis, this project is at much earlier stage of development (Phase II).

5.1. Background and Clinical Need

The intubation project began as a response to the clinical need proposed by Dr Gabriella Iohom and Dr Peter Lee, consultant anaesthetists at Cork University Hospital, as part of the UCC Biomedical Design module. Following proposal of an initial concept design in 2013 by one of the BioDesign groups which failed to offer a viable solution to the clinical need, the author began to start researching potential solutions as part of this PhD (2014). The following sections will detail the unmet clinical need and detail the development activities carried thus far which is now in Phase II of the design control process.

5.1.1. Endotracheal Intubation

The first step in Phase I of the design control process is to investigate in more detail the clinical need (identified by the clinicians in this case) and to define a problem statement. One of the most common difficulties encountered in anaesthesia is airway intubation. Endotracheal intubation involves placing an endotracheal tube (ETT) into the patient's trachea to create an artificial air passage for breathing (see Figure 5.1). Typically an ETT is used on patients under-going surgery to provide for the administration of anaesthesia, when ventilation of the lungs is necessary, or in an emergency when a patient is injured and has lost the ability to breathe independently. The traditional approach consists of inserting an ETT through the mouth or nose, using a Macintosh laryngoscope (direct laryngoscopy). The tube placement follows a non-trivial trajectory, through the mouth/nose, past the vocal cords, into the trachea and not the oesophagus.

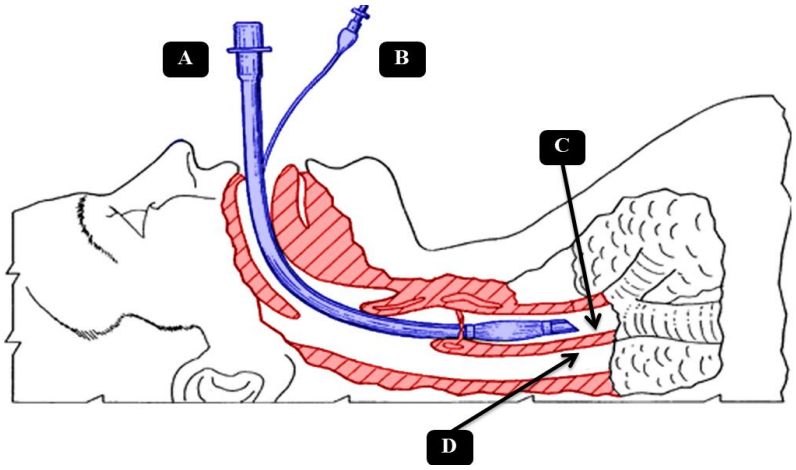


Figure 5.1 Endotracheal tube (A) and inflation cuff (B) inserted into the trachea (C) avoiding the oesophagus (D) [122]**.**

A flexible stylet or "bougie" is often inserted through the centre of the endotracheal tube during introduction to enable navigation. Intubation may be performed by individuals with varying levels of medical experience and skill levels. Less experienced clinicians have far lower intubation success rate (typically 80% [123]). In addition, a patient's trachea region may be obstructed, or the anatomic path from the mouth to the trachea may be tortuous. Conventional intubation devices and techniques may cause damage to tissue within the patient's airway leading to swelling or bleeding. Failed, difficult, or delayed intubation is a primary cause of litigation claims and failure to intubate is reported in 1 in 50-100 cases [124].

Difficult tracheal intubation (DTI), which is associated with grades 3 & 4 airway access classification (see Figure 5.2), may lead to oxygen desaturation, hypertension, dental damage, admission to ICU, complications at extubation, arrhythmias, bronchospasm, airway trauma, CICV, and the sequelae of hypoxia (cardiac arrest, brain damage, and death) [125].

Figure 5.2 Direct laryngoscopy grading system [126], [127]**.**

Laryngoscopy performed in the operating theatre under controlled circumstances carries a risk of difficult intubation in up to 10% of cases [128], [129]. Unfortunately, physical findings on examination of the airway discriminate poorly between potentially easy and difficult intubations [130], [131]. Thus, anaesthetists need to be prepared for the unanticipated difficult airway. In addition, there are circumstances that lend themselves to a high risk of difficult laryngoscopy and tracheal intubation, such as emergency intubations outside the operating theatres, (e.g., emergency departments, and intensive care units). For a list of complications see Table 5.1 and Table 5.2.

Table 5.1 Summary of complications and incidence rates from Cook and MacDougall-Davis [132]**.**

Complication	Incidence	Clinical setting	Knock on effect
Can't intubate can't ventilate (CICV)	1 in 5,000	General anaesthetics	Emergency surgical airway (ESA)
Emergency surgical airway (ESA)	1 in 50,000	General anaesthetics	25% of anaesthesia-related deaths
Emergency surgical airway (ESA)	1 in 600	Emergency department (ED)	Failure results in risk of death
CICV requiring ESA	1 in 200	Emergency department (ED)	25% of anaesthesia-related deaths
Minor complications - e.g. difficulty with direct laryngoscopy	0.5-1%	General anaesthetics	Rarely of great clinical consequence
Failed intubation	1 in 1,000 - 2,000	Elective setting	Failure to intubate
Failed intubation	1 in 250	Rapid sequence induction (RSI) in the obstetric setting	Failure to intubate
Failed intubation	1 in 50 - 100	Emergency department (ED), intensive care unit (ICU), and pre-hospital	Failure to intubate
Direct tracheal intubation (DTI) (grade 3 and 4)	10.10%	General	Failed laryngoscopy in 0.1%
DTI occurrence with previous DTI	24%	General	Intubation failed in 30% of previous DTI
Increase risk of DTI due to obesity (BMI>35 kg m^{-2})	Odds ratio + 1.34	General	Increase risk of DTI
Increase risk of DTI due to absence of neuromuscular blocking agents	Odds ratio + 1.48	General	Increase risk of DTI
Adverse events (general)	3.70%	General	14% of events lead to death

Table 5.2 Main categories of injury claims associated with respiratory events from American Society of Anaesthesiologists Closed Claims Project (ASACCP) [132]**.**

Injury claim	% of claims	Clinical setting
Inadequate ventilation	38%	Non-emergency surgery
Oesophageal intubation	18%	Non-emergency surgery
Difficult tracheal intubation (DTI)	17%	Non-emergency surgery

Anaesthetists are increasingly turning to video laryngoscopes for normal as well as difficult tracheal intubations in both the elective and emergency setting. Compared to standard direct laryngoscopy, these devices offer better views of the airway, require less force to intubate the trachea, and facilitate guidance of a trainee by sharing the view of the airway with the instructor [129]. Despite these advantages, limitations remain. Better airway inlet visualization does not translate into increased success with intubation [133]. For example, it is impossible to intubate the trachea in 4% of patients using a Glidescope (a type of video laryngoscope) despite a satisfactory glottis view and the use of a preformed stylet or flexible introducer [134]. Reasons for failure include (i) the inability to manoeuvre the endotracheal tube into the trachea or (ii) the endotracheal tube abutting the anterior portion of the larynx when using the stylet [129]. While use of an expensive fibrescope or bronchoscope overcomes these challenges [135], such technology is not always accessible or financially supported.

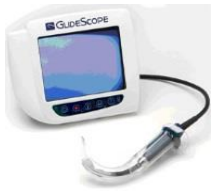
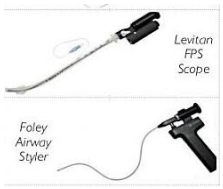
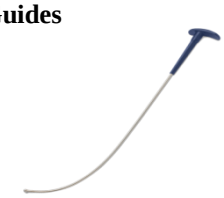
5.1.2. Current Technology

The endotracheal market is a rather crowded one. The standard laryngoscope handle and blade is the most common instrument used to elevate the tongue and mandible to allow visualization of the cords. The blade can be straight (Miller) or curved (Macintosh). Miller blades are usually reserved for paediatric patients while most physicians use a Macintosh blade for adults (see Table 5.3). The blade must be long enough to reach the vallecula (the space between the base of the tongues and the epiglottis). Once correctly positioned, the blade is used to guide the endotracheal tube into position.

A malleable stylet can also be used in conjunction with the laryngoscope to aid ETT insertion. The stylet is inserted inside an endotracheal tube to make it more rigid, or to change the shape of the tube. For example, the tip of the endotracheal tube can be bent slightly to facilitate passage through the cords. It is recommended that the stylet be used in all emergency intubations. In this way, if the shape of the tube needs to be modified, the stylet is already in place. The stylet should be lubricated prior to insertion into the endotracheal tube, so that it is easy to remove.

Technology specifically designed to aid in difficult intubation includes video laryngoscopes, fibreoptic lighted stylets, flexible tube guides, endoscopes and steerable guides. Table 5.3 compares the perceived advantages and disadvantages associated with these technologies.

Table 5.3 Comparison of commercially available technology.

Technology Name	Key Features / USP	Strengths / Advantages	Weaknesses / Disadvantages
Standard Laryngoscope 	The traditional global standard for tracheal intubation and successful in most standard cases (*Multiple vendors including Welch-Allyn, Smiths, Flexicare, Medline etc.).*	Reusable, low cost per use, robust and virtually unbreakable.	Not reliable for difficult intubation, requires multiple sizes, risks of sterilisation, no working channel.
Video Laryngoscope 	Direct visual confirmation of intubation in real-time *(Multiple products including V-Mac and C-Mac (Karl Stortz), Ascope (Ambu), Glidescope (Verathon), McGrath (Aircraft/ Covidien).*	Direct visualisation of the larynx and airways, compatible with customised stylets (Ambu, Verathon).	High initial purchase cost ($10,000), not always available, not always successful in accessing visually identified larynx.
Fibreoptic Lighted Stylets 	Lighted stylet provides transabdominal lighted confirmation of entry *(Multiple products including Bonfils & Brambrink (Karl Stortz), Shikani, PocketScope & Levitan (Clarus Medical), Tube-Stat (Medtronic).*	Visual confirmation by means of the transabdominal light position.	Expensive (compared to flexible tube guides) - $100-150, infection risk with re-use, no multiple sizes, no working channel, lack of control and manoeuvrability.
Flexible Tube Guides 	Flexible devices provide a low-cost reposable or disposable alternative to visual verification. *(Multiple products including Aintree, Frova & Arndt (Cook), GlideRite (Verathon), OptiShape (Truphatek), single-use Bougie (Smiths).*	Low cost ($5-45), soft Coudé tip (Smiths), reusable (Cook, Verathon, Thruphatek), malleable, multiple sizes available (Cook).	Lack of control (no tip deflection), pre-formed or fixed shape on insertion, unreliable, infection risk on re-use, concerns of mechanical robustness (GlideRite).
Intubating Endoscopes 	These flexible intubating endoscopes allow the ET tube to be mounted coaxially. The scope intubates the trachea and the tube is slid forward *(Several products, reusable and disposable, such as Ambu aScope).*	Cost per intubation using a reusable or a disposable has been calculated by Ambu to be slightly more than $300. They are most useful for planned difficult intubations.	Shafts are often unnecessarily long to allow for variations in anatomy. Can be difficult to release the ET tube without assistance. Considered expensive compared to many technologies.
Steerable Tube Guides 	Steerable Stylet used to position ETT during intubation. Very few products available. E.g. Rapid Positioning Intubation Stylet (RPiS) *(Airway Management Enterprises).*	When combined with VL, the RPiS has the ability to flex and retroflex the distal tip which can improve access for the solo practioner during difficult intubation.	Lack of human factor design, limited functionality, relatively high market price cost of $200 (discounted price of $178.60 available through certain distributors).

5.2. Design Definition and Development

From reviewing the clinical need and current solutions which attempt to meet that need, it became clear that a potential gap exists in the intubation market. Difficult tracheal intubation, which may result in failure to intubate, occurs in 5.8% of cases for the overall population and 15.8% for obese patients [131]. Current solutions are either ineffective (a flexible bougie) or vastly too expensive (endoscopes) to have on hand in case of an emergency situation. Based on end-user feedback (see Section 5.3.3), the single greatest limitation with current introducers and scopes, is the lack of control at the tip to effectively steer the endotracheal tube to the target area. Despite being able to now visualise the airway using video laryngoscopes, the physician still cannot manoeuvre the tip around the epiglottis into the trachea. Therefore a solution which can match the manoeuvrability and control of a high-end endoscope, but with the cost effectiveness of a flexible tube glide, may present a very attractive value proposition to the health care sector.

5.2.1. Problem Statement

Develop a cost efficient, dynamic means to improve ease of airway intubation allowing for controlled distal tip manipulation to navigate around the epiglottis while being capable of use in conjunction with a visual means such as a video laryngoscope.

5.2.2. Design Criteria and Concept Solution

As illustrated in Figure 5.3, the concept ideation process converged quite quickly on a means of creating an articulating distal tip with an ergonomic control handle. The principal design input requirements were to develop a solution to the defined problem statement which includes:

- An outer diameter and length to receive a wide range of ETT sizes.
- Distal tip deflection in both the up and down directions to a maximum of 90°.
- Quick engagement and release of the ETT.
- Ergonomic and intuitive to use.
- Left and right, single handed use.
- Minimal setup/assembly.
- May be used with video laryngoscopy.

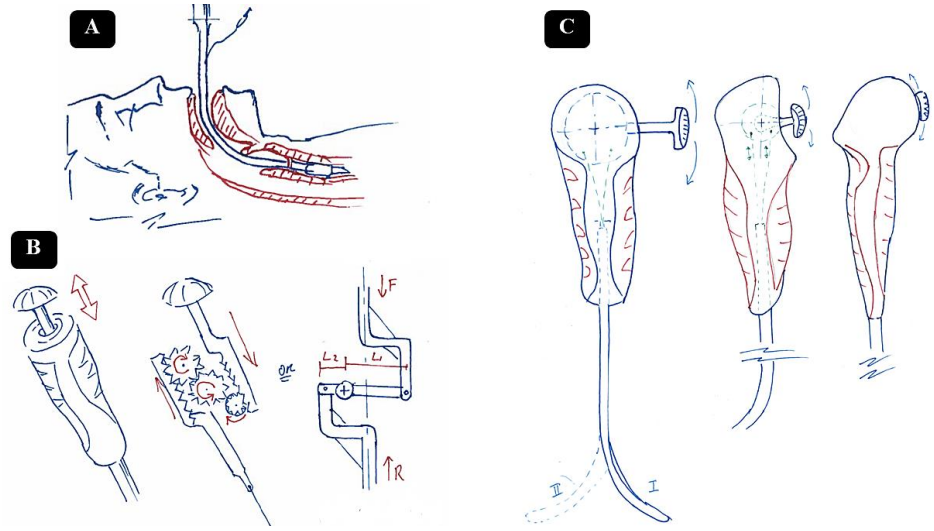


Figure 5.3 Intubation concept ideation with A) understanding the anatomical constraints, B) single handed plunger concept with gearing or linkage distribution, and C) single handed thumb dial actuated concepts.

The design criteria included producing a solution which could be used for a wide range of endotracheal tube sizes. The rule of thumb when sizing the ID of an ETT is: $ID = \frac{age\ in\ yrs}{4} + 4$. Therefore, adopting a similar design as the SecuRetract construction (Chapter 3), a 5mm OD tube configuration may be suitable to children and adults from the ages of 4 years and up. The initial focus is on the adult population and further design iterations may be subsequently pursued for new-borns, and infants. A number of different methods of transferring an axial force and handle designs were considered to allow positioning over the patient's airway (similar to a bronchoscope).

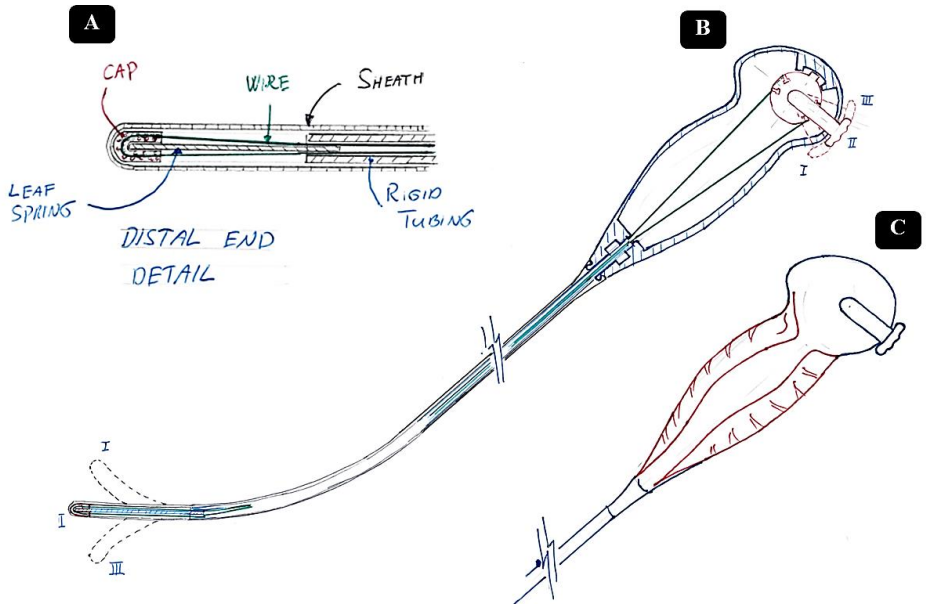


Figure 5.4 Design concept for an intubation delivery device with perspective view (C) and cross sectional detail (A and B) developed by the author as part of this PhD.

5.2.1. Design Development

The design concept, which was developed as part of this PhD, comprises a shaft, control handle and articulating distal tip (Figure 5.4 and Figure 5.5). The shaft terminates with a leaf-spring actuator, which leverages the existing solution for single-plane actuation employed in the SecuRetract device. The leaf spring may be displaced in two directions, ($\pm 90^{\circ}$) by engaging one of two wires thus providing dynamic tip articulation. The wires continue from a cap fastened to the distal end of the leaf spring to a dial built within the control handle. The leaf spring returns to the original straight position once the dial in the control handle has been released. A flexible sheath covers over the shaft and clips onto the control handle providing an air-tight encasement. The overall length of the shaft must be long enough to suit a range of ET tubes. Adult tubes can be 30 cm long. Therefore, the device must be long enough to pass the 30 cm long tube over the shaft and to allow sufficient additional length to extend the articulation tip beyond the sheathed ETT.

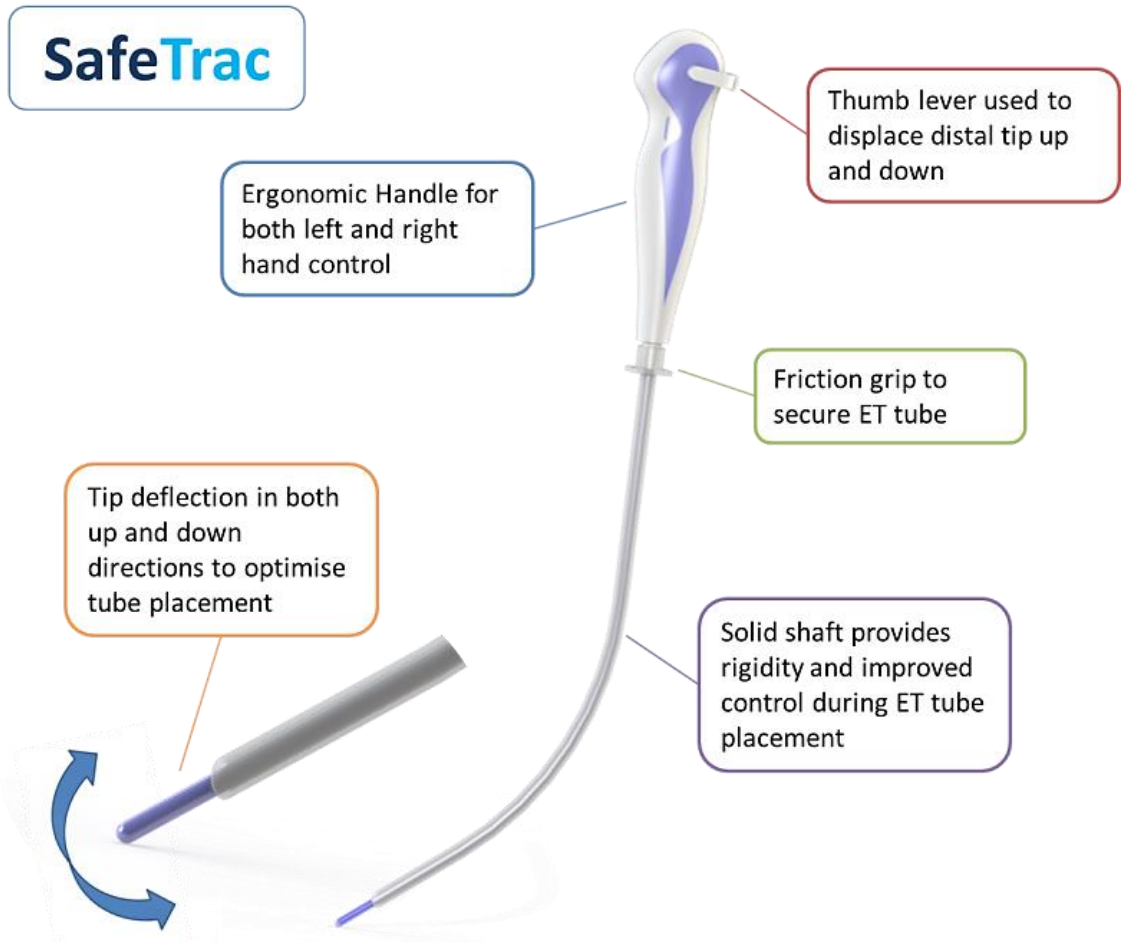


Figure 5.5 Proposed solution to enable safe intubation with key features highlighted.

The design of the control handle was inspired by conventional endoscopes and may be used in either the left or right hand of the user. The length of the grip space on the handle was based on anthropomorphic data. The hand breath for males from the 1st to the 99th percentile varies from 8.2 – 9.6 cm, and for females from 6.9 – 8.6 cm [136]. Therefore a handgrip length of 8 cm was decided to accommodate both the male and female population. The original sketches were rendered and detailed using SolidWorks®.

To use SafeTrac, firstly the ETT is sheathed over the shaft of the device. A tapered friction grip at the handle's base secures the ETT in position but provides for easy release of the ETT when required. The ETT and device are inserted into the patient following the airway profile until the distal tip of SafeTrac is positioned in the larynx (vocal cords). The device's thumb-actuated handle provides an intuitive user-interface for actuation and positioning of a pre-formed rigid shaft which extends beyond the ETT length. The shaft's leaf spring actuator facilitates single-plane articulation of the distal tip around the epiglottis and larynx, enabling easy positioning of the tip within the trachea. Once the tip of the ETT is steered into position within the trachea, SafeTrac is withdrawn and the ETT is advanced as required following conventional means for assessing correct placement of the ETT within the patient's airway (i.e., using the graduations along the length of the tube to estimate placement depth, inflating cuff and checking for effective seal). A video laryngoscopy may be used to aid in visualising placement. However this is not necessary, and conventional standard laryngoscopes may be instead used to obtain a view of the vocal folds and the glottis during administration.

Figure 5.6 Exploded view of SafeTrac handle render in SolidWorks.

5.2.2. Concept Prototype Evaluation

Based on the strength of the concept design, along with the market feedback which will be discussed in Section 5.4, the SafeTrac project progressed to Phase II of the design control process whereby initial prototype development and evaluation took place. Computer aided drawings were used to produce rapid-prototyped solutions developed using in-house facilities. The handles were printed using fused deposition modelling (FDM) and comprised of five parts (see Figure 5.7). The left

hand housing accommodates the central shaft securing it at the distal end of the handle. A cam insert in the proximal end provides an axial displacement of a wire tendon, operably connected to the articulation tip, and which provides a deflection of at tip of ± 90°. The handle further comprises a lever to rotate the internal cam, the matching right hand housing and a fastening cap used to tighten the right and left sides together.

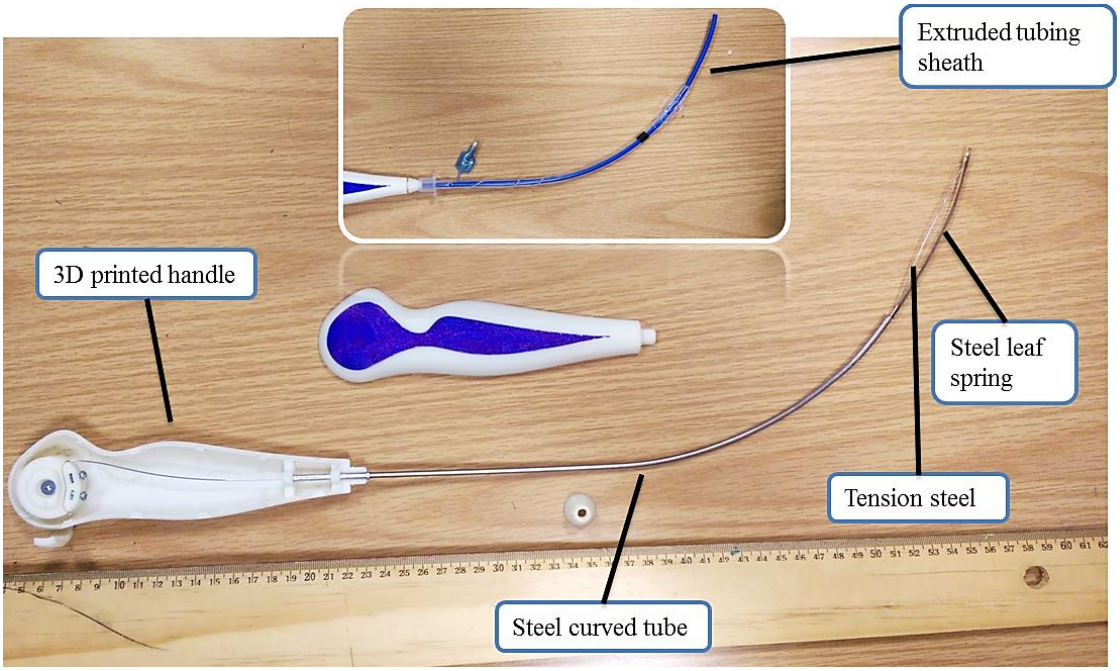


Figure 5.7 Prototyped solution shown in the deconstructed position, and assembled position insert.

The shaft comprises a stainless steel (grade 316) hypo tube with an OD of 4.2 mm, bonded to a spring member (0.4 mm thick stainless steel grade 301) and sheathed with a polyurethane extruded tubing. The bonding process used silver solder with an overlap length of 25mm to provide a large and easily bonded interface well in excess of the recommended single lap-joint overlap distance (3t – 6t). Bench top trials indicated that an axial force of approximately 25N is required to displace the 80mm long spring member 90° (vertical displacement of 51mm). The distal portion of the hypo-tube has a curve with a radius of curvature of 180mm in line with the curvature of a standard ET tube. This aids in positioning SafeTrac in the airway. The resulting early-stage prototype was suitable for proof of concept evaluation.

The prototype was evaluated in a simulated clinical setting using an Ambu® Airway Management Trainer at South Infirmary Victoria University Hospital, Cork. This manikin model simulates the tongue, epiglottis and pharynx with semi-soft material enabling qualitative feedback on device performance. Two consultant level anaesthetists (Dr

Gabriella Iohom and Dr Peter Lee) compared the traditional rigid laryngoscope, flexible bougie delivery and the SafeTrac device. The GlideScope video laryngoscope was used to visualise navigation around the epiglottis. The purpose of the evaluation was to get user feedback on the usability and design of the device.

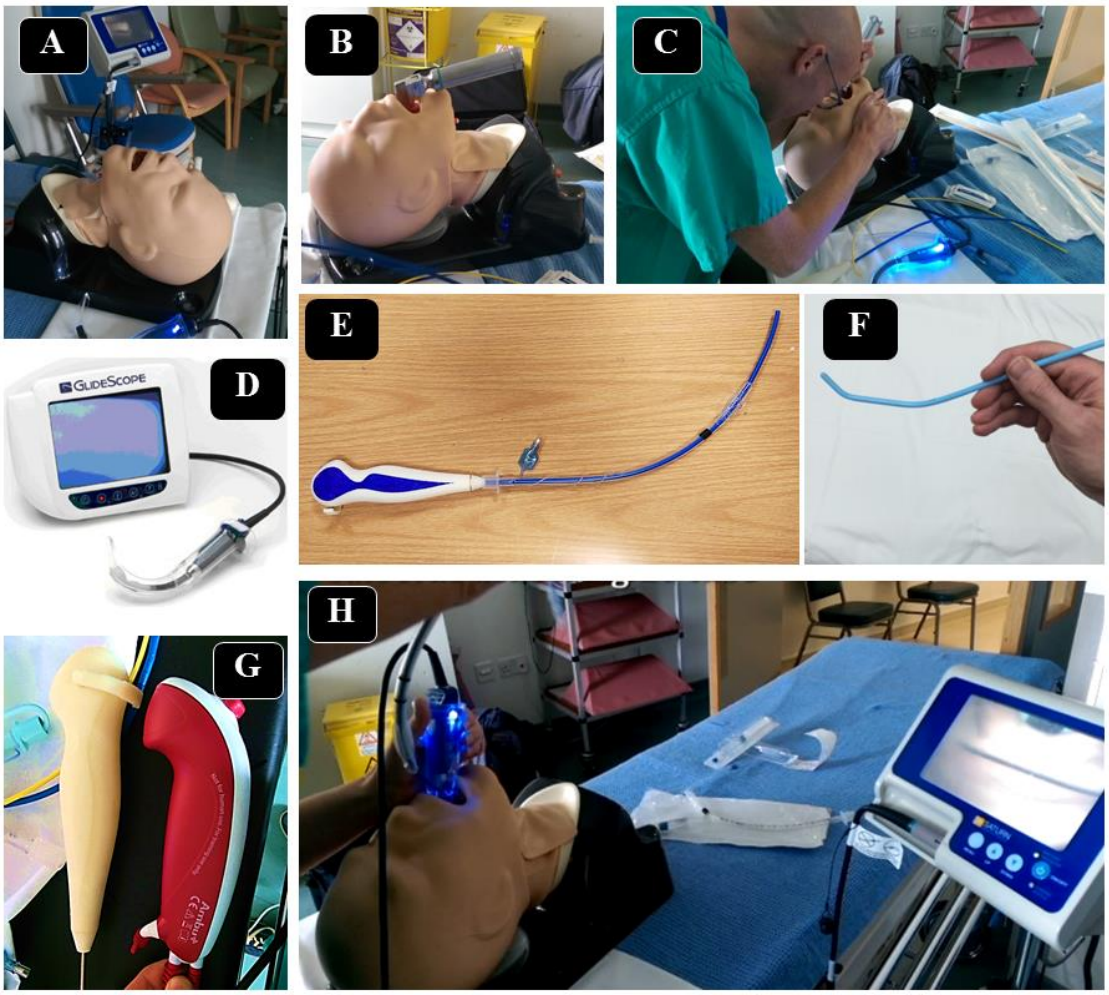


Figure 5.8 Simulated clinical testing using a respiratory manikin: A) Ambu® Manikin, B – C) laryngoscope delivering ETT, D) GlideScope video laryngoscope, E) SafeTrac prototype, F) flexible bougie, G) steerable flexi scope, H) SafeTrac delivering ETT.

Both physicians noted the significantly improved user interface and control associated with the SafeTrac compared to the flexible bougie. The distal end of SafeTrac could be quickly steered into the trachea avoiding the oesophagus much more easily than the bougie. The Manikin did however have several limitations. The rubber nature of the material used to produce the manikin was quite stiff and less compliant than biological tissue. The rubber finish presented a significant friction coefficient, compounded by the lack of moisture that would be present in a live model, resulted in an almost sticky sensation when trying to slide the ET tube off the device into the trachea.

The evaluation also identified some key design limitations and recommendations with the presented SafeTrac prototype. A release ring/lever may be included to dislodge the ETT with the user's fourth finger from the tapered interface. The rigidity of the shaft should be increased. It was noted that whilst introducing the ET tube with SafeTrac, the user would apply a bending moment due to the stiff nature of the rubber manikin that would deform the central steel shaft. A stiffer hypo tube material or one with a greater wall thickness is therefore required. The overall handle size was also scaled to 90% of the original length (see Figure 5.9). Finally, a significant amount of force (>25 N) is required to displace the distal end. This force is difficult to apply with such a small thumb lever on the handle. Therefore, a larger lever distance or a geared internal mechanism may be required to reduce the force requirements on the user. Further design refinement is required at Phase II of the design control process with a greater emphasis on user requirements and design for manufacture before the alpha or "basic" prototype is identified and assessed prior to moving onto the next Phase of product development.

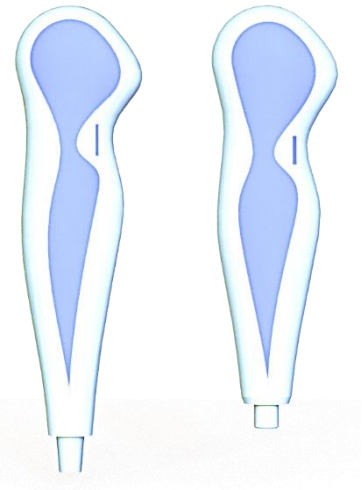


Figure 5.9 Reduction in handle size based on feedback from prototype evaluation.

The device's usefulness both with and without the video laryngoscope was noted where SafeTrac was successfully deployed with the use of a GlideScope as well as a standard laryngoscope with equal ease. It should be noted however, that the users were extremely experienced and in the opinion of the author, it would be easier to introduce SafeTrac under video guidance. Video footage is available at the following link: https://youtu.be/YfmozaCyogg.

5.3. Simulated Analysis

The manikin trial also identified a significant failing in the concept prototype. After repeated use, the spring member attached to the distal end of the hypo tube failed and fractured immediately after the solder bond (see Figure 5.10). This failure coincides with the fixed end and area of maximum stress for a flat spring member. Analysis was subsequently carried out to characterise the theoretical stress in the system and to identify a possible configuration to prevent permanent deformation.

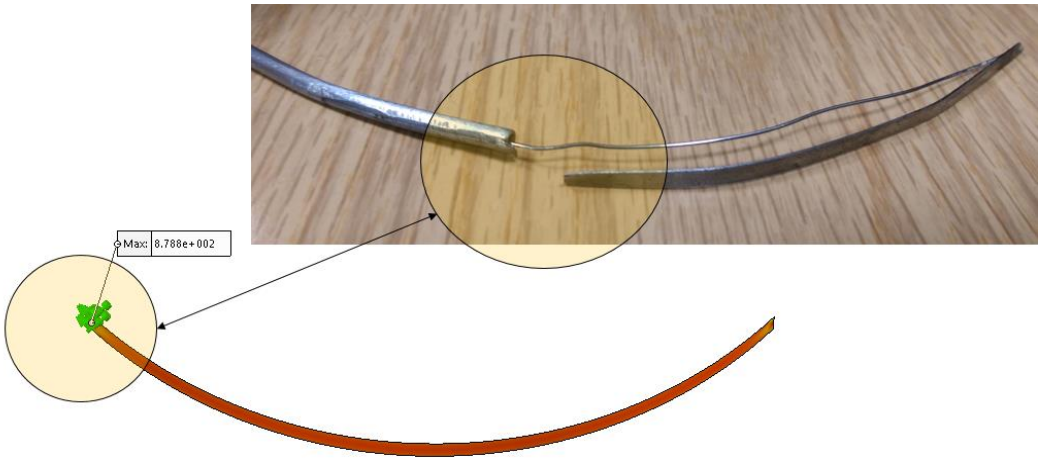


Figure 5.10 Fractured spring member at point of maximum stress at the fixed end of the compliant member.

A nonlinear solver in SolidWorks® was used in this analysis. The main difference between a linear and nonlinear analysis, is that an iterative approach is used to solve nonlinearity allowing a change in model stiffness and variable loading, as each iteration is ran independently. Nonlinear simulations also account for the actual material properties such as yielding which is ignored in the linear approach (Hooke's law). A system is considered nonlinear if the stiffness and external force vector are no longer linear. The equation for nonlinear analysis is therefore given by $[K(u, F(u))]\{u\} = \{F(u)\}$, where the stiffness matrix [K] is the function of displacement {u} and external force vector {F}. In the case of a flat spring member fixed at one end, the external force vector is changing constantly as the member curves about the axis of rotation. In addition, large displacements lead to a change in stiffness as the model's shape adjusts from a straight to a curved profile, resulting in geometric nonlinearities.

The simulation model comprised a flat member matching the prototype geometric properties for length and width (L=80mm, W=3.3mm), and varying thickness's (t= {0.4, 0.3, 0.2, 0.15 mm}) to analyse a range of configurations. The members were fixed in both translation and rotation at one end, and a rotation condition of 3.14 radians was created at the opposite end. The simulation ran one hundred step increments to evaluate in detail the effect of curvature from 0°, past the desired 90° and all the way to a fully curved 180° beam (see Figure 5.11). The maximum deflection required to navigate around the epiglottis is estimated to be between 60-90°. However, in the case that the spring member is physically extended beyond the operational parameters, the simulated model was extended up to a deflection of 180°

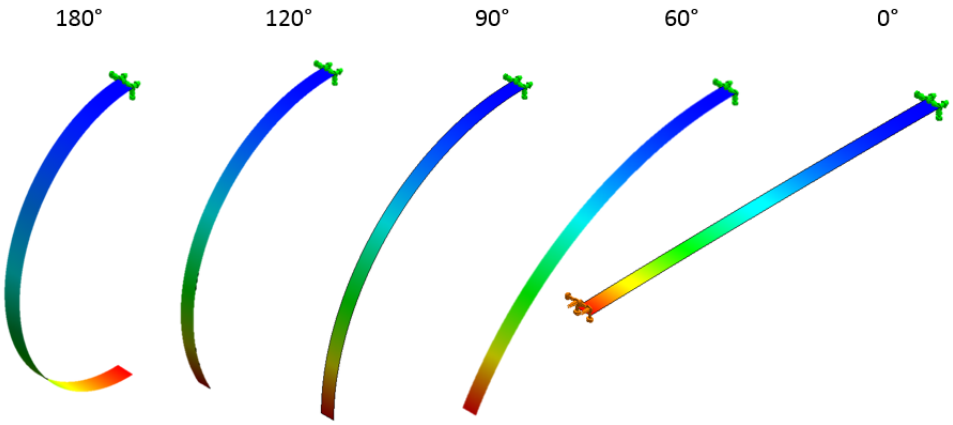


Figure 5.11 Nonlinear simulation of a curving flat wire beam from 0° to 180° ran by the SolidWorks® Simulation add-in.

5.3.1. Simulation Results

Table 5.4 provides an overview of the maximum stress experienced in the simulated system at the fixed end of the model. As expected, with reducing beam thickness, and corresponding moment of inertia, the bending stress is likewise reduced. The material selected for the analysis was 301 stainless steel with an elastic modulus of 197 GPa to match the physical model [137]. At a thickness of 0.4mm and a curvature of 90 degrees, a bending stress of approximately 877MPa which is greater than the material's yield strength of 515 MPa [137]. In fact, this simulation indicates that the bending system with yield at a curvature only 54°.

Table 5.4 Simulated maximum bending stress (MPa) corresponding to a given beam thickness and deflected angle from fixed end of spring member.

Thickness (mm)	Deflected Angle (°) 180	120	90	60
0.4	1756	1159	877	579
0.3	1236	814	617	407
0.2	826	545	412	272
0.15	620	408	310	204

Based on this nonlinear simulated analysis for 301 stainless steel spring member with the given geometrical constraints, a material thickness of 0.2 mm would remain within the elastic region of a stress strain curve up to a curvature of approximately 112° (see Figure 5.12). A thickness of 0.2 mm is typically the thinnest sheet stocked by suppliers and is readily available.

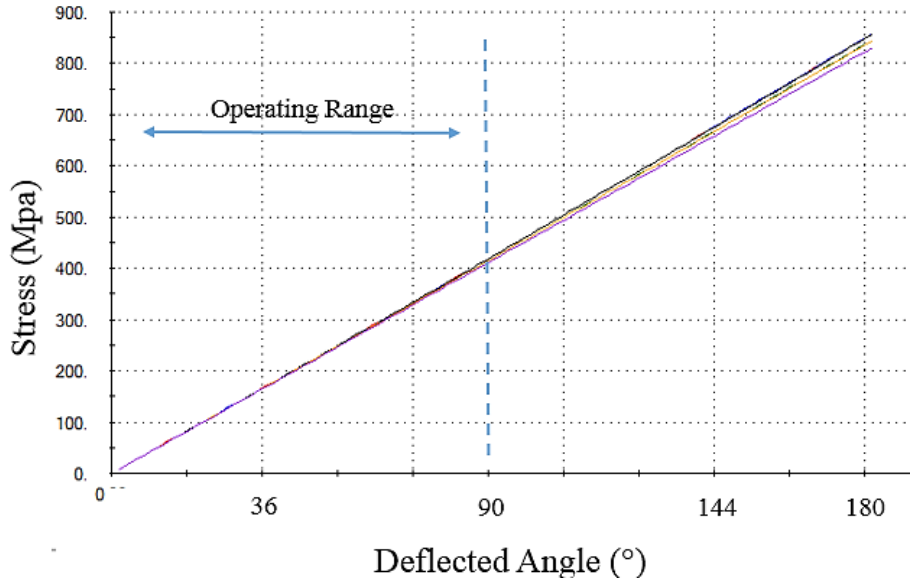


Figure 5.12 Simulated bending stress with increasing angle of deflection for a 0.2mm thick 301 stainless steel with a modulus of 197 GPa.

An alternative approach to adjusting the material thickness is to identify a material with a greater yield strength to prevent permanent deformation during the operational limits. Table 5.5 lists selected steels from the SolidWorks® material library with yield strengths up to 710 MPa. Processes such as hardening and tempering increases the material yield strength but also makes the material more brittle. Whereas processed such as annealing has the opposite effect. An example of a cold-formed full hard 301 stainless steel can have a 0.2% yield strength of up to 965 MPa [138] which would indicate that it would remain in the elastic limit but would require significantly greater axial force to create the desired curve. Further analysis is required to carry out both simulated and physical testing with additional materials. However, based on this analysis, and for ¼ hard 301 stainless steel with a yield strength of approximately 515 MPa, a 0.2 mm thick sheet would remain elastic within the operational limitations below a curved angle of 90°.

Table 5.5 Select steel materials evaluated in the nonlinear simulation with values corresponding to those provided by the SolidWorks® material library.

Material	Elastic Modulus (GPa)	Tensile Strength (MPa)	Yield Strength (MPa)
AISI 4340 steel (normalised)	205	1110	710
Alloy steel (SS)	210	724	620
AISI 1045 steel (cold drawn)	205	625	530
AISI 4340 steel (annealed)	205	745	470
201 annealed SS	207	685	292
AISI 316 SS sheet	193	580	172

5.4. Commercial Feasibility

The intubation project was awarded an Enterprise Ireland Feasibility funding in 2015 (CF-2015-0241-Y). The deliverables of the feasibility fund were to carry out in-depth market and customer research, and to ultimately determine the commercial potential of SafeTrac. This funding vehicle is complementary to the design control process and simply supports the design teams engagement with key opinion leaders which ultimately is used to define the clinical need, establish the design criteria, and populate the market requirement specification during Phases I.

5.4.1. Intubation Market Size Assessment

According to a market research report published by Markets and Markets, the total global anaesthesia and respiratory devices market was worth $12.7 billion in 2015 [139]. Globally there are an estimated 65 million annual intubations performed[130], [131]. Based on an estimate of 1 in 10 intubations requiring an assistance device [131], [132], the total potential market lies at 6.5 million units per year. Approximately 85% of intubations occur during non-emergency surgery and 15% are in the emergency room or ICU [140]. Between 3% and 17% of all intubations may be classified as difficult [130], [131]. In the obese population it is approximately 14% [141]. With increasing levels of obesity and associated co-morbities, the intubation market is estimated to grow at a compound annual growth rate of 9% (radian insights, 2014).

Difficult intubations are also reported in children. According to the 4th National Audit Project by the Royal College of Anaesthetists in UK, difficult intubations account for 9% of all intubations in emergency departments (EDs) in paediatric age group. These statistics call for the provision of a difficult airway trolley (DAT) dedicated to paediatric use in all emergency departments [142]. There is no particular difference between the incidence of tracheal intubation difficulties in USA and European countries, as various studies from UK and USA have reported comparable rates ranging from 1-12 % [143].

5.4.2. Commercial Opportunity

SafeTrac is applicable to two significant market segments within the overall intubation and laryngoscopy market. These include:

- Cases where an unexpected difficulty arises during direct laryngoscopy or video laryngoscopy

- Cases which are expected to be difficult due to known patient characteristics and in which video laryngoscopy is planned.

In both of these markets, the technology for ETT guidance and placement includes bougies and stylets which cannot provide the required manoeuvrability in cases of difficult positioning. The proposed device has the potential to allow intubation without upgrading from direct laryngoscopy to video laryngoscopy or, in the case where video laryngoscopy is already deployed, from video laryngoscopy to the intubating endoscope.

In this environment, a commercial opportunity exists to bring SafeTrac to the market as an intermediate-cost endotracheal introducer that may be used in conjunction with video laryngoscopes. This device has the potential to displace bougies and stylets as the standard of care for intubation. Manufacturing costs of SafeTrac are estimated at $20-$25 allowing an end-user price of $100 and a gross margin around 75-80%, an acceptable industry standard. When used in combination with a video laryngoscope (costing approx. $15 per disposable blade), as an alternative to an intubating scope, considerable savings per case of up to $195 are feasible (i.e. $115 versus $270-$310).

5.4.3. Key Opinion Leader Feedback

Four leading experts and influencers in anaesthesiology were interviewed as part of the clinical assessment of SafeTrac (see Figure 5.13). The key opinion leaders were selected based on their extensive publication history in areas of airway management and difficult tracheal intubation. The interviews took place over telephone communication and were recorded for posterity. Prior to each interview, the experts was furnished with material information and a video of use as described in Section 5.2.

Figure 5.13 Clinicians interviewed as part of SafeTrac's assessment.

Each of the clinicians were enthusiastic about the technology and encouraged further development. Some of the main comments included:

- "This device could work with that more difficult anatomy."
- "The big advantage of this particular instrument that you have is that now once you are in you can get it to deflect down to go down into the trachea."
- "I think over all the idea is a great idea. Passing the tube is the biggest problem we see with video laryngoscopes and this idea is a good one."
- "This is something that makes it easier for the operator to advance the tube but I like the idea and there is need for it."
- "It certainly looks as though you offer something different to other devices that are currently on the market and available."
- "A potential niche for this is that not everyone has a fiberscope. This would be a useful adjunct."
- "If you can make a disposable one that is higher quality than the competitors and yet it's reasonably priced then why wouldn't people go for this."

The major negative point expressed by the interviewees relates to pricing as SafeTrac would essentially be displacing existing cost effective solutions such as the common bougie. Therefore, in order to gain traction, a low manufacturing cost solution which can demonstrate clinical and economic benefit during ET tube placement, particularly during difficult tracheal intubation, is essential.

5.4.4. Intellectual Property Review

The elegant design of the proposed solution fits neatly between the high end / high cost steerable video bronchoscopes and the low tech / low functionality bougies and stylets (e.g. Gliderite). A provisional patent review has identified a number of disclosures competing in this space [144], [145]. Many of the identified patents have been filed over 20 years ago and therefore are no longer protected. These disclosures describe a means of articulating a distal tip, typically relating to the field of cardiovascular studies and diagnosis (see Figure 5.14). Freedom to operate on certain aspects of the SafeTrac design is therefore reasonable. However, through the future design and

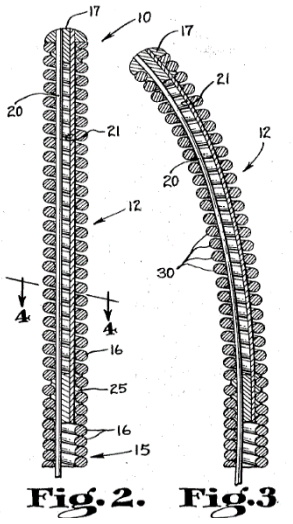


Figure 5.14 spring guide identified during IP review (US patent number 3,521,620).

development of SafeTrac, a number of innovative and non-obvious features will be added to secure IP protection to set this invention apart from the treats of competitors (e.g., smart sensing (CO_2, pH) within the steerable tip). Additional design features include an ergonomic handle with torsion spring return and a friction grip taper to engage the proximal end of an ET tube, as well as the facility for single-handed ETT deployment.

5.4.5. Regulatory Pathway

Through partnership with an independent regulatory expert (IncraMed, Galway Ireland), an appraisal of the regulatory classification and pathway was carried out which again fed into the market requirement specification during Phase I of the control process. The main purpose of this engagement was to verify the authors review following the medical device directives and FDA guidelines and to establish the future requirements towards regulatory approval. However, it should be noted, that independent reviews are not required as one can self-certify device classifications, but in this instance, the activity was supported by the Enterprise Ireland Feasibility award.

US FDA Product Code Review

a) Based on preliminary product concept specifications this review has identified the FDA Product Code BSR as likely to be applicable to the device.
b) The code corresponds to FDA Regulation number 868.5790, tracheal tube stylet.
c) In accordance with the requirements of this regulation number the device is Class I in the United States.
d) No premarket notification application and FDA clearance is required before marketing the device in the U.S. However, manufacturers are required to register their establishment with FDA.
e) No clinical data should be necessary for this device but a Clinical Evaluation Report including an examination of published literature and similar devices is recommended.

EU Classification and Approval Feasibility

a) In order to market a medical device on the European market it must bear the CE mark and conform to the requirements of 93/42/EEC as amended by 2007/47/EC.

Article 9 of the directive classifies devices as Class I, IIa, IIb and III. Classification is determined in accordance with Annex IX of the directive.

b) As an invasive device for transient use (i.e. normally intended for continuous use for less than 60 minutes) the device is Class I in accordance with Rule 5. i.e. "All invasive devices with respect to body orifices are in **Class I** if they are intended for transient use."

c) In accordance with the MDD, article 3, an Essential Requirements review will be necessary to meet Annex I.

d) In order to affix the CE mark, an EC declaration of conformity in accordance with Annex VII will be required before placing the device on the market.

e) Based on Annex VII there is no requirement to;

- Lodge an application with a notified body for assessment of the Quality System.
- Lodge an application for examination of the technical documentation for the product.

5.5. Chapter Review

This chapter outlines the early stage design and development of an endotracheal tube introducer, which may answer a clearly defined clinical need and has received positive end-user feedback on the clinical utility.

5.5.1. Technical and Commercial Review

The early stage solution presented in this chapter called SafeTrac comprises a manoeuvrable distal end to facilitate ease of endotracheal tube placement. The articulating tip affords the operator the control to navigate around the epiglottis exposing a direct route to the trachea. Conventional stylets lack the manipulation required for first time accurate placement, reducing the risk of dental damage, admission to ICU, complications at extubation, arrhythmias, bronchospasm, airway trauma, awareness, CICV, and the sequelae of hypoxia. This is particularly useful for obese patients with a BMI > 35 kg/m^2, patients with DTI, and patients with a torturous anatomic path from the mouth to the trachea.

Unlike alternative devices, this solution comprises specific features that allow it to be used in conjunction with video laryngoscopes (VL) in a complementary fashion that provides an external view of tube placement. VL is quickly becoming the standard of care

in intubation but cannot manipulate the tip of the tube independently and may require SafeTrac to aid in tube placement.

Despite only beginning the Phase II development cycle, key opinion leader feedback and market assessments point to a large unmet market which may be future exploited by the SafeTrac device. While not finalised, the current solution provides a good basis for IP protection with significant manoeuvrability and controllability coupled to a rigid shaft. Future design analysis will seek to improve stability of the current shaft and bending member, optimise the ETT friction grip at the handle's base, and minimise part count and assembly costs downstream. In order to present meaningful advantages over competitors, clinical utility must be first validated and key differential features over conventional introducers must be further developed to build a compelling IP portfolio.

5.5.2. Design Control Review

Unlike the SecuRetract and ProDural projects (Chapters 3 and 4), the SafeTrac project was developed from the get-go within the design control process. This involved following the phased flow charts of the development cycle summarise in Chapter 2. During Phase I, the author was able to propose a number of concepts to solve the clinical need presented in Section 5.1 as well as conducting preliminary commercial and legal assessments. This was compiled into a Market Requirement Specification (MRS) which subsequently served as the foundation of an Enterprise Ireland application (Commercial Feasibility Award as described in Section 5.4). The CF award was used to progress the IP, regulatory and commercial know-how to the current stage of development. However, the MRS is not designed to be exclusively used to attract funding. The primary object of the MRS is to present a report to the principal investigator to decide on whether a project is worth formally pursing further within a controlled framework. In the case of SafeTrac, where the origins were firmly rooted in a clinician identified need, and a rapidly expanding commercial market, the project was approved for further development.

As the first project to be fully implanted under the design control process, the author experienced for the first time the difficulty in complying with all the procedural requirements. For example, under good documentation practices typically implemented in R&D environments, a laboratory notebook must be routinely

reviewed by the Principal Investigator. Design review meetings with independent observers must be routinely scheduled. Risk analysis should be reviewed and approved from a medical point of view from a clinician / medical expert. All of these activities required significant time and personnel management to coordinate scheduling, which can be difficult in even the smallest design teams. Furthermore, for small teams, the time to initiate and begin to archive documents as part of the design history file can be quite burdensome. This burden may be offset with a dedicated quality administrator.

The SafeTrac project and its QMS implantation has only begun initiation and significant work is still required to generate a documents within a design history file to facilitate translation into the clinical environment. Further financial and personnel resources will be required to progress SafeTrac along the project life-cycle before a clinically and commercially attractive proposition is achieved. The current level of progression is qualitatively summarised in Table 5.6.

Table 5.6 SafeTrac project progression.

Phase Activity Completion	Phase I	Phase II	Phase III	Phase IV	Phase V
	Clinical Need Definition	Design and Development Plan	Detailed Requirements Specifications	Design Transfer / Pilot Production	limited Market Release
	100%	50%	0%	0%	0%
	Concept Solutions / Early Risk Assessment	Define Design Inputs	Manufactures / Suppliers Identified	Final Design Validation	Post-Market Surveillance
	100%	50%	0%	0%	0%
	Early Commercial / Market Assessment	Initiate Quality Documentation	Risk Assessment Update / Implement Risk Controls	Complete DHF, DMR, Technical File	Sales and Physician Training
	100%	25%	0%	0%	0%
	Early Intellectual Property Review	Build and Evaluate Prototypes	Verification & Validation Protocols	Artwork / Traceability	Expand Sales Effort
	100%	20%	0%	0%	0%
	Early Regulatory Assessment	Expanded IP landscape Review	Build Units for V&V	Market Launch Strategy	Continuous Improvement
	100%	50%	0%	0%	0%
		Risk Analysis Update	Process Validation Plan	Manufacturing Qualification	Quality Audits
		20%	0%	0%	0%
		Define Regulatory Requirements	Confirm Intellectual status	Regulatory Approval	
		100%	0%	0%	
		Business Plan	Update DHF / Business Plan	Build Inventory / Scale Up	
		25%	0%	0%	

Chapter 6 Radiopaque Pulmonary Tumour Model Development

This chapter details additional work completed by the author relating to the development of radiopaque tumour models in bronchoscopy. This research relates to a larger research project within the Biomedical Design Research Group at UCC, which aims to develop a semi-automatic bronchoscopic navigation system for pulmonary disease biopsy. The work described in this chapter was not conducted within the design control process as it was initially solely an exercise in academic research without clinical or commercial intent. However, this work does present the opportunity to investigate how an already established project may be retrospectively introduced into a quality system and presents novel developments which may serve to advance training in bronchoscopy.

6.1. Background and Clinical Need

This work relates to the design and development of a number of contrasting tumour models that may be endoluminal deployed in the lung and are clearly identified under CT imagery. This project was a response to a need to produce identifiable and retrievable tumour models that can be used for *ex vivo* and *in vivo* evaluation of a semiautomatic bronchoscopic navigation platform [10]. The clinical need was presented by Doctors Marcus P Kennedy and Kashif Ali Khan (respiratory medicine) and represents a collaborative effort between UCC's School of Engineering and Cork University Hospital, and sought to develop a means to evaluate the effectiveness of a novel tracking system, but also which may be used during bronchoscopic training. The results from this work were subsequently published in the Journal of Bronchology and Interventional Pulmonology [12].

6.1.1. Radiopaque Tumour Markers

Radiopaque markers or fiducials are a point of reference in CT imaging and are used clinically to mark sites for biopsy or resection [146]. Solid markers such as gold spheres and radiopaque clips have been described in the literature [147], [148]. However the purpose of this work was to investigate a model which mimicked soft-tissue to target lesions and to evaluate a novel virtual bronchoscopy system [13], [149]–[151]. Despite reported attempts, an effective pulmonary tumour model capable of being sampled using standard bronchoscopic techniques to confirm successful localisation of the nodule has yet to be developed [152], [153].

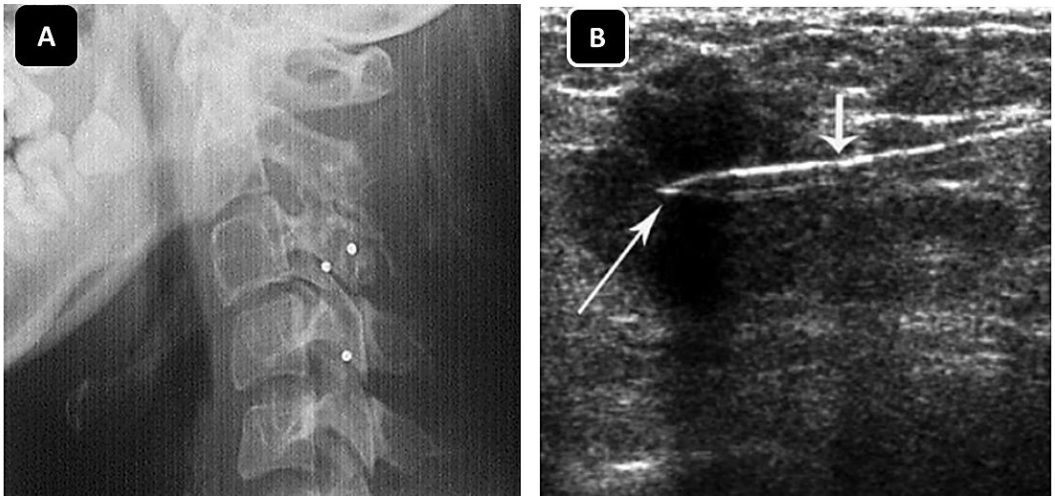


Figure 6.1 A) an example three gold sphere markers implanted into the vertebral bodies [147]**, and B) a breast sonogram showing an introducer and radiopaque clip marker in a solid mass** [148]**.**

Tissue-mimicking materials have been commercially developed to test ultrasound equipment with similar attenuation and speed of sound properties to soft tissue by modelling the tissue as an isotropic, homogeneous material. Large silicone based training systems such as Blue Phantom™ have been developed to accurately replicate the ultrasound behaviour of anatomy simulation. However, these are high cost systems and have yet to be applied as implantable / injectable fiducial markers. Common commercial materials include urethane rubber, condensed milk and hydrogels [154]. Hydrogels are the most frequently used models [146] and comprise of a network of hydrophilic polymer chains. An example of an injectable hydrogel is polyethylene glycol (PEG). PEG is an inert chemical widely used in pharmaceuticals, cosmetics and medical devices [146] which has a paste-like consistency in the body and slowly liquefies before being absorbed [146]. While easily deployed and mimicking the acoustic properties of soft tissue [146], [155], the fact that PEG does not congeal to form a bulk-like substance means that it is unsuitable to mimic soft tissue tumours.

Gelatin is among the earliest materials used for soft-tissue mimicking. Gelatin is a colourless, foodstuff derived from collagen that sets to a homogenous gel on cooling. While representative of soft tissue acoustic properties, reported disadvantages with this mixture include instability with varying temperature, susceptibility to microbial invasion, and difficulty in evenly distributing the graphite scatters, glass microbeads or silica during cooling [156], [157].

Another popular hydrogel is agarose [157]–[159]. Derived from agar, agarose obtains bulk-like consistency with low attenuation of ultrasound and high tensile strength [158], [160]. Agarose is readily available as a white powder which easily dissolves in near-boiling water, forms a gel when cooled [161], and has acoustic properties (speed of sound between 1498-1600 m/s) [157] comparable to soft tissues such as muscle, tendons, ligaments, fascia, fat, and fibrous tissue (average 1561 m/s) [157]. However agarose has not been previously endoscopically deployed as a tumour model.

The aim of this work was to develop novel radiopaque tumour models and to quantifiably assess the appropriateness of the models as clinically relevant analogues to pulmonary lesions. A further objective of this work was to identify methods to test the artificial tumours that accurately reflect the *in vivo* clinical environment. Such tumour models may have an application in bronchoscopic training by providing radiopaque

markers for the trainee to target, as well as providing a testing method to evaluate emerging bronchoscopic imaging and navigation systems.

6.1.2. Agarose Tumour Model Development

Based on the review described in Section 6.1.1, agarose was selected as one of two tumour models based. Agarose's similar acoustic properties to soft tissue, its ready availability, and its ease of fabrication made it an attractive first material to review as part of this work. Agarose type I-A used in this work (Sigma Aldrich), has a gel strength >2500 g/cm^2 at 1.5% concentration and a gel point of 36±1.5°C [162]. The protocol for developing the agarose tumour models followed a trial and error approach beginning with adopting previously published recipes [158], [159], [163]. The focus was to develop a mixture with low viscosity at relative low temperature (40-50°C) to facilitate *in vivo* endobronchial injection with a high contrast medium for CT.

Four agarose-based models (A-D) were evaluated. As a comparison, the first model (A) recreated the recipe proposed by Chmarra *et al*. (2014). To enhance the visibility of the models under magnetic resonance imaging, an iodine–containing contrast, Omnipaque™ (GE Healthcare, Buckinghamshire, U.K.) was included in all subsequent models. The final agarose mixture (model D) also contained the preservative dimetridazole [164] (Sigma-Aldrich, St. Louis, MO, USA), an anti-protozoan used in human foods, which lengthens shelf-life of the tumour models by preventing nucleic acid synthesis of micro-organisms [165].

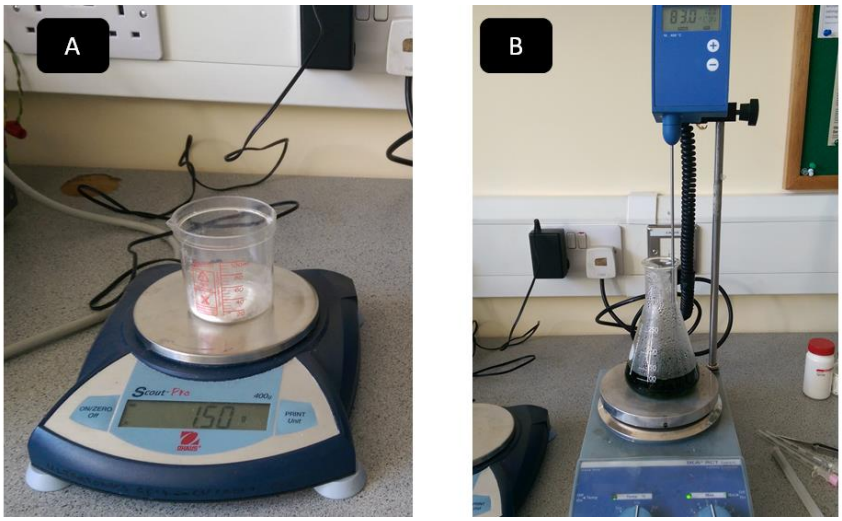


Figure 6.2 Method for developing agarose based tumour models demonstrating A) measuring reagents and B) mixing and heating composition.

The reagents and quantities for the investigated agarose model compositions are listed in Table 6.1. The compositions were prepared by combining and heating the mixture above 95°C to bring the components into a well-mixed and heated solution (IKA® RCT Safety Control Magnetic Stirrer). The mixture was allowed to cool to 50°C before being transferred into 25 ml air tight sample containers. The tumour samples were then cooled in a fridge overnight to yield a firm elastic material with a dense gelatin-like consistency.

Table 6.1 Composition of reagents used in agarose tumour models.

	Model A	Model B	Model C	Model D
Agarose (A0169 SIGMA) [g]	7.5	2	1.5	1.5
Glycerol (99% GC SIGMA) [ml]	30	10	nil	nil
Sephadex® (G2580 SIGMA) [g]	4	nil	nil	nil
Omnipaque™ 300mg I/ml [ml]	nil	4	10	20
Dimetridazole (D4025 SIGMA) [g]	nil	nil	nil	1
Food colouring [ml]	0.1	1	0.75	0.4
Distilled water [ml]	158.4	83	87.75	77.1

6.1.3. Tripe Tumour Model Development

Motivated by undocumented but anecdotal reports from the project's clinical advisors of its usage, the second novel model investigated was beef tripe, a sponge-like edible offal from the chambers of the bovine stomach. Tripe, a soft tissue in its own right, acts as a scaffold for contrasting medium and offers an elastic structure that may resemble a pulmonary tumour once endobronchially deployed (see Figure 6.3).

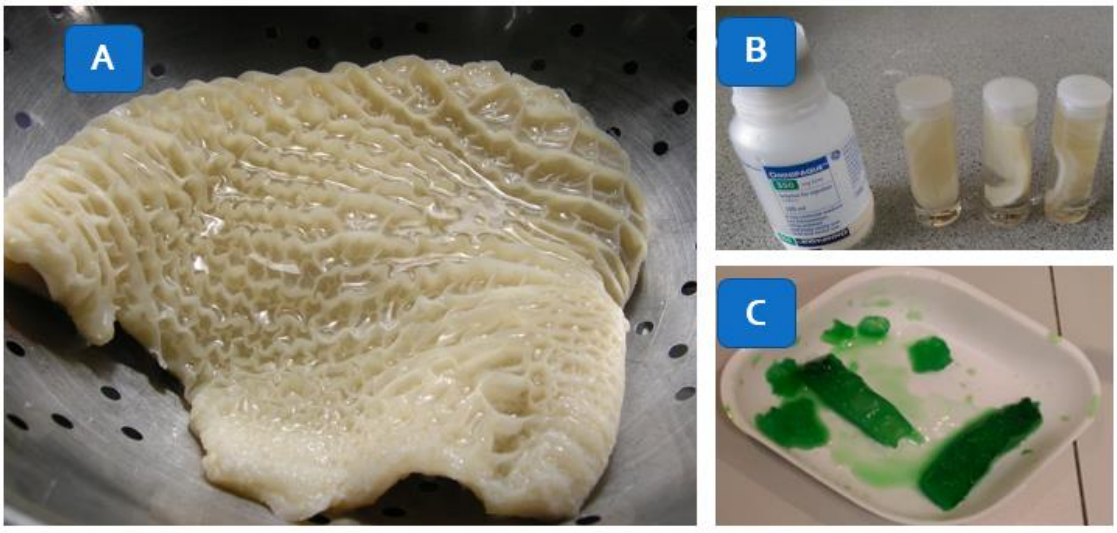


Figure 6.3 Beef tripe (A) prepared into segments soaked in Iodine (B) and enriched in food dye prior to use (C).

The locally sourced beef tripe (A O'Reilly & Sons, English Market, Cork) was prepared by cutting the tripe into 50 mm rectangular segments and placing the segments into 25 ml containers filled with iodine (Omnipaque™ 350mg I/ml) and food colouring. The softer superficial layer extending from the denser lining of the tripe was removed leaving a homogenous, elastic consistency. The samples were left to soak overnight and were further injected with iodine immediately before use. The mechanical properties of each of the agarose samples and the tripe material were not characterised as part of this work as the primary objective was to create a detectable radiopaque mass for bronchoscopy, whereby properties such as stiffness and elastic modulus were not essential to the application. Furthermore, the mechanical properties at varying concentrations have already been well documented [166].

Table 6.2 List of physical models used to evaluate the various tumour model types.

	Evaluation Method		
Model Type	Chicken Fillet	Swine Lung	Pre-Clinical Investigation
Agarose A	✓	-	-
Agarose B	✓	-	-
Agarose C	✓	✓	✓
Agarose D	-	✓	✓
Tripe	-	-	✓

6.2. Tumour Model Evaluation

The physical simulations used to evaluate both the agarose and tripe models are listed in Table 6.2. The first three agarose tumour models (A-C) were evaluated in a soft tissue explant (chicken fillet) and the resulting CT images (120 kVp, 650 mA, slice thickness 0.6 mm) were assessed for CT contrast (GE Discovery VCT PET/CT 64 Slice CT Scanner) following direct injection through a 21 gauge aspiration needle (SmoothShot TBNA NA-411D-1321, Olympus). An experienced end user (radiology technician / clinician) then reviewed the CT images to verify the resulting scans resembled *in vivo* soft tissue. The agarose samples were first heated to bring them into a solution before being injected into separate models for comparison.

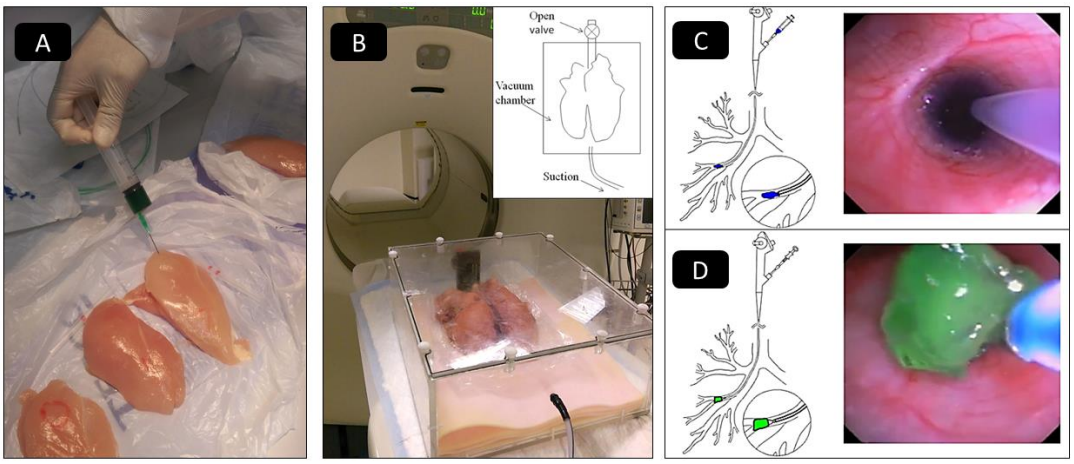


Figure 6.4. A) Agarose tumour model injection into soft tissue explants (chicken fillets), B) vacuum chamber and swine lung model with implanted tumours being scanned with CT, C) placement of tumour models during pre-clinical investigation with diagram and endoscopic image of agarose model placement and D) diagram and endoscopic image of tripe tumour placement.

Agarose models C and D were evaluated in an inflatable swine lung model [13]. The preserved swine lung was inflated in a vacuum chamber and held at a constant vacuum to achieve inflation (see Figure 6.4 B). Eight tumour models (four of each sample) were injected by an experienced operator into the left and right lungs, in the upper, middle and lower lobes. A bronchoscope (Olympus Evis Exera BF - 1T160) and adapted Olympus SmoothShot with the needle removed to increase flow through the catheter were used. Each model was injected in the liquid form before cooling to a radiopaque mass. The swine lung was subsequently scanned (inhalation and exhalation) using CT to determine the tumour model's detectability.

6.2.1. Soft Tissue Explant Investigation Results

CT imaging illustrates the clinically-relevant contrasting ability of the agarose models A, B and C compared to the background intensity of the chicken model (see Figure 6.5). In each instance, a vial containing the model mixture was placed next to the tissue analogue. Model A, which recreated Chmarra's *et al*. (2014) work closely resembles the attenuation characteristics of the soft tissue chicken model. In the CT image, there is little or no discernible difference between the agarose and the surrounding soft tissue. The Hounsfield Units (HU) (scale to describe radiodensity) measured 85±8 HU, similar to that of the liver (60HU). However, models B and C, which include the contrast medium Omnipaque™, demonstrate stark contrast between the tumour model and the tissue (see Figure 6.5 A-D).

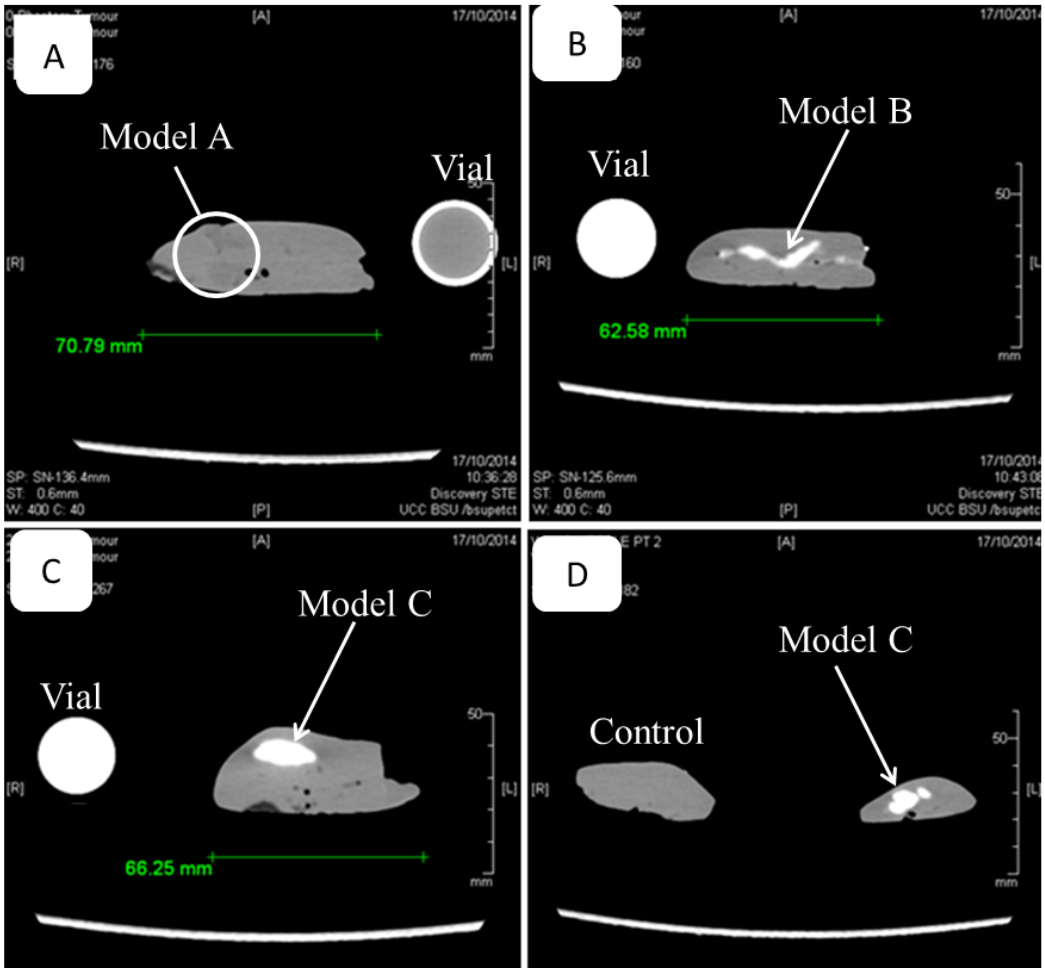


Figure 6.5 Assessment of tumour models in a chicken fillet with A) model A as proposed by Chmarra *et al*, B) model B with 4ml of Omnipaque, and C) model C with 10 ml of Omnipaque. D) Illustrates a comparison between model C and a baseline (no tumour).

6.2.2. Swine Lung Model Investigation Results

The resulting CT image from the swine lung model was overlaid with an airway reconstruction using 3DSlicer [11], [167]–[170] software platform and captured images from the bronchoscopic feed (see Figure 6.6). The sites targeted with the increased contrast agent (i.e. model D at points c, e, f, h) demonstrated greater contrast to those of model C (i.e. reduced contrast agent at points a, b, d, g). Site (a) shows a slight dispersion of model material similar to a circumferential endobronchial lesion. This sample was placed using the sheath from a modified 21 gauge SmoothShot aspiration needle. Well placed endobronchial fiducials of good size ($\approx 15mm^3$) resembling cancerous lesions can be observed in all the remaining sites with some locations completely obstructing airway segments ((e) and (g)). The mean time-to-placement was 2 minutes with a further 5 minutes required before the samples congealed to form a dense tissue-like nodule.

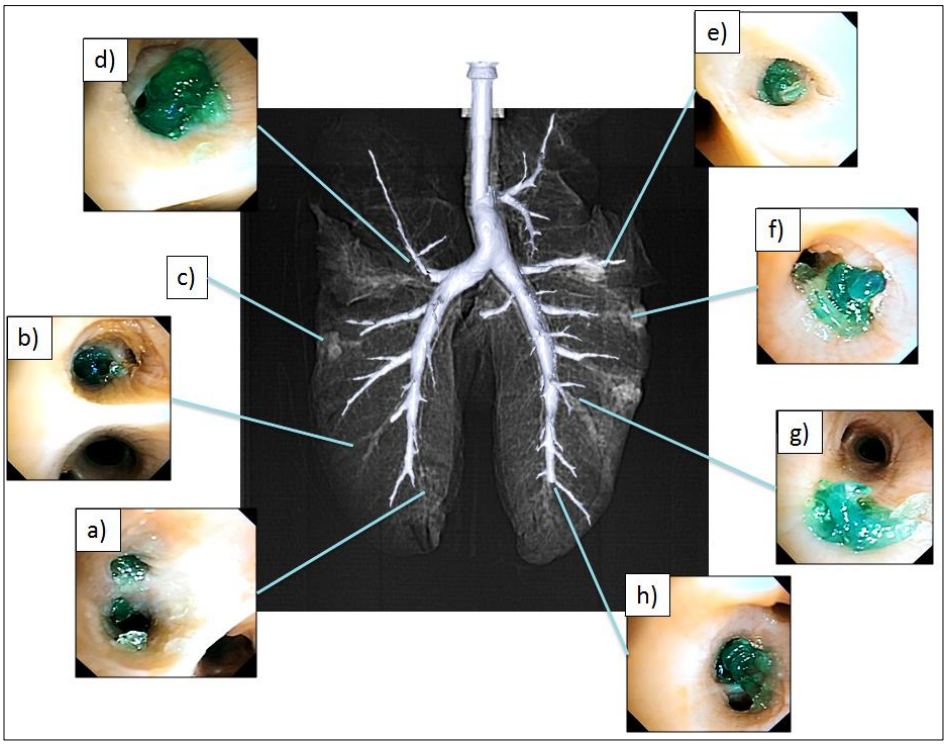


Figure 6.6. CT image from inflation swine lung overlaid with video bronchoscopic images. Sites a, b, d & g contain agarose model C, and the remaining sites contain agarose model D.

6.2.3. Pre-Clinical Animal Investigation Procedure

Agarose tumour models (C and D) and the tripe model were evaluated *in vivo* during pre-clinical porcine investigations (n=3). The models used were landrace swine (18, 22 and 40 kg) which were sedated for the duration of the experiment and euthanized immediately following the procedure without recovery. The investigations were approved by both the Irish Department of Health (approval no: B100-4441) and UCC Ethics Committee (approval no: 2012-17) and were conducted by respiratory clinicians.

The study end-points were to qualitatively evaluate the ease of use of administering the models and to assess their accuracy and efficacy in simulating soft-tissue pulmonary tumours. During the study, the animal was subject to CT imaging before and after model insertion. CT scan parameters were 0.625 mm slice thickness, 0.625 mm slice separation and tube current of 60 mA at 120 kV with standard kernel reconstruction. The agarose tumour models were again heated on a hotplate magnetic stirrer before cooling to 38-45˚C for multiple injections by an experienced endoscopist (6 for n=1, 8 for n=2 and 1 for n=3). The insertion temperatures were derived from earlier bench top trials where the mixture temperature was allowed to cool in controlled incremental steps and a corresponding sample was injected through a 21 gauge sheet until no longer possible.

Each agarose model, with an approximate volume of 4±1 ml, was injected transluminally using a 21 gauge SmoothShot aspiration needle, and endoluminally with a 1.8 mm catheter via luer access port (see Figure 6.4). After each injection, the catheter was removed and the working channel was flushed with cold (4 ˚C) saline solution to promote rapid coalescence of the tumour model, confirmed by camera visualisation.

Iodine-enriched tripe tumour models were introduced through the endotracheal tube with the bronchoscope and endoscopic biopsy forceps (Radial Jaw™ 4, Boston Scientific). The tripe models (0.7±0.2 cm^3), were positioned in the upper right, lower right, upper left, and lower left lobes with real-time fluoroscopy (BV Pulsera, Philips) to confirm placement. Both agarose and tripe models were sampled endoscopically subsequent to CT imaging.

6.2.4. Pre-Clinical Investigation Results

The first pre-clinical investigations examined the use of agarose model C as a radiopaque lung tumour marker. As illustrated Figure 6.7, a single large contrasting nodule, 15 mm long, is visible in the middle lobe of the right lung. A pneumothorax (partial lung collapse) of the left lung is also evident. This pneumothorax was likely caused due to trauma during transbronchial model insertion. Over-advancement of the needle may have breached through the pleural membranes leaking ventilated air into the thoracic cavity causing the pneumothorax. The use of transbronchial placement in subsequent animal trials was limited to reduce the risk of further pneumothoraxes. Scarring of the internal structure was also observed as a result of the heated (65˚C) material on insertion prompting subsequent trials to use lower injection temperatures (38-45 ˚C).

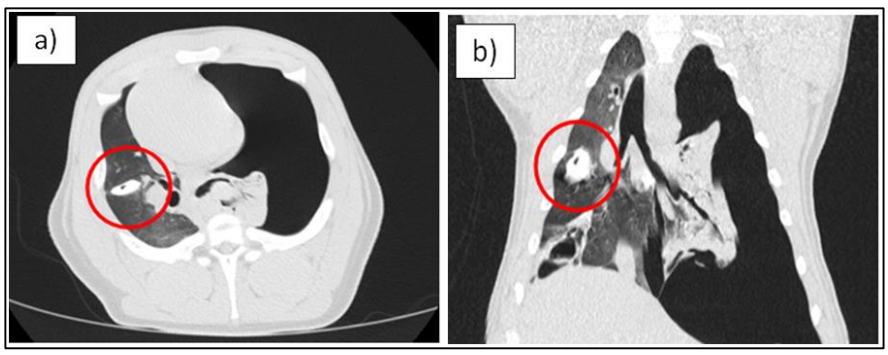


Figure 6.7 CT slice images from the first pre-clinical investigation illustrating a slice through the a) Transverse and b) Coronal plane, of an agarose tumour model measuring approximately 15 mm in length positioned in the middle right lobe.

Subsequent animal investigations evaluated agarose model D, as well as the iodine-enriched tripe model. Tumour models were identified by visual CT inspection. Figure 6.8 compares CT images taken before and after model tumour placement during the second animal investigation. Three different agarose tumour sites are noted, with stark contrast where detected. As with the swine lung model, the average time-to-placement was 2 minutes. However of the eight locations targeted, only three are clearly visible. Instead of creating structured fiducials when placed in the upper airways, the agarose model appeared to coat the airway wall as it passed deeper into the bronchial passages reducing its radiopacity. This was most likely a result of slower time-to-coalescence as the core body temperature is only slightly lower than the gelling temperature of agarose. At a concentration of 1.5%, agarose has a gel point of 36±1.5°C [162], which may be sufficient for human use (37°C). However, the porcine model has a higher normal body temperature of 38.7-40°C. The insertion temperatures were reduced in the third trial.

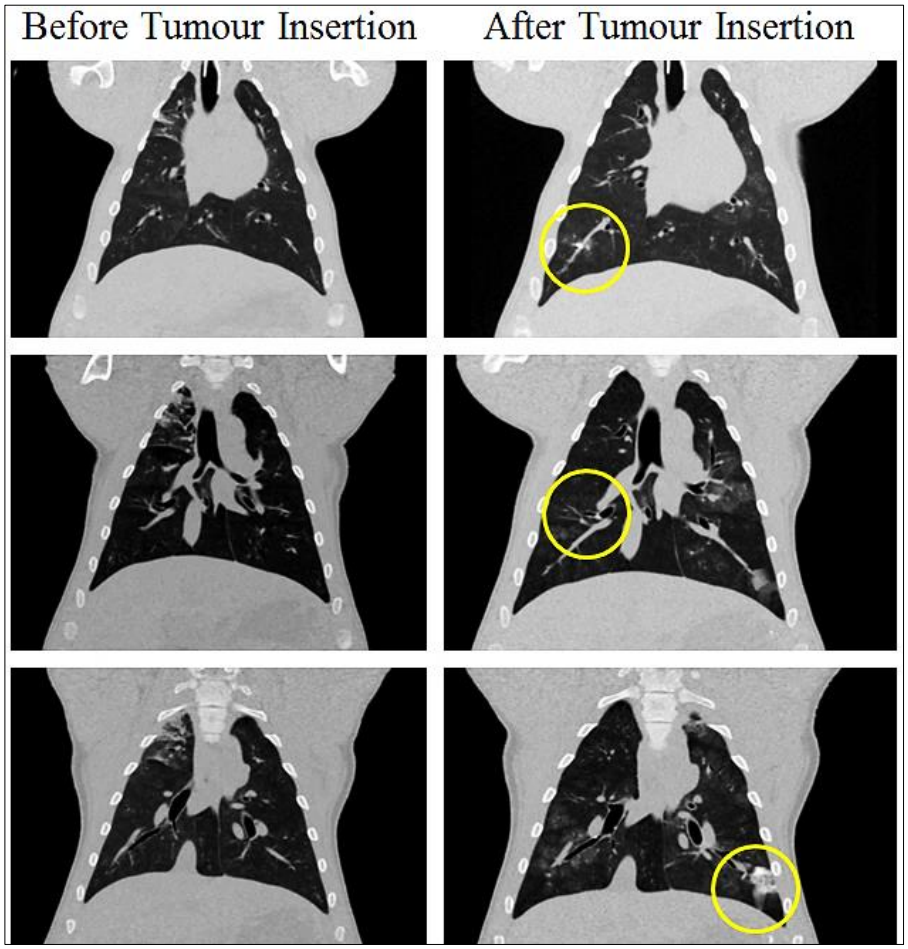


Figure 6.8. Resulting CT images taken before and after tumour model insertion during the second pre-clinical animal investigation. Areas of visible contrast circled in the right column are absent in their corresponding pre-tumour images in the left column. The areas indicated are sites where the agarose based models were deposited.

Unlike the agarose model, the tripe model exhibited a clear and vivid contrast under CT imaging resembling tumour like obstructions with definite structure during the second trial. Figure 6.9 compiles a number of different imaging techniques to identify and locate the tripe models. The background image is a picture of a CT scout (scanogram) as used for planning every scan slice. The scout clearly identified the position of two radiopaque tripe models in the left and right lower airways measuring approximately 20 mm in length. The average time taken to place a tripe tumour was approximately 2 minutes. A detailed slice along the coronal plane through the models is also pictured in the upper left image of Figure 6.9 illustrating the stark contrast of the models against the background image density. The models were placed under real time fluoroscopy and the resulting c-arm image is pictured in the lower left region of the image. The remaining two images picture the tripe models before and after endobronchial insertion.

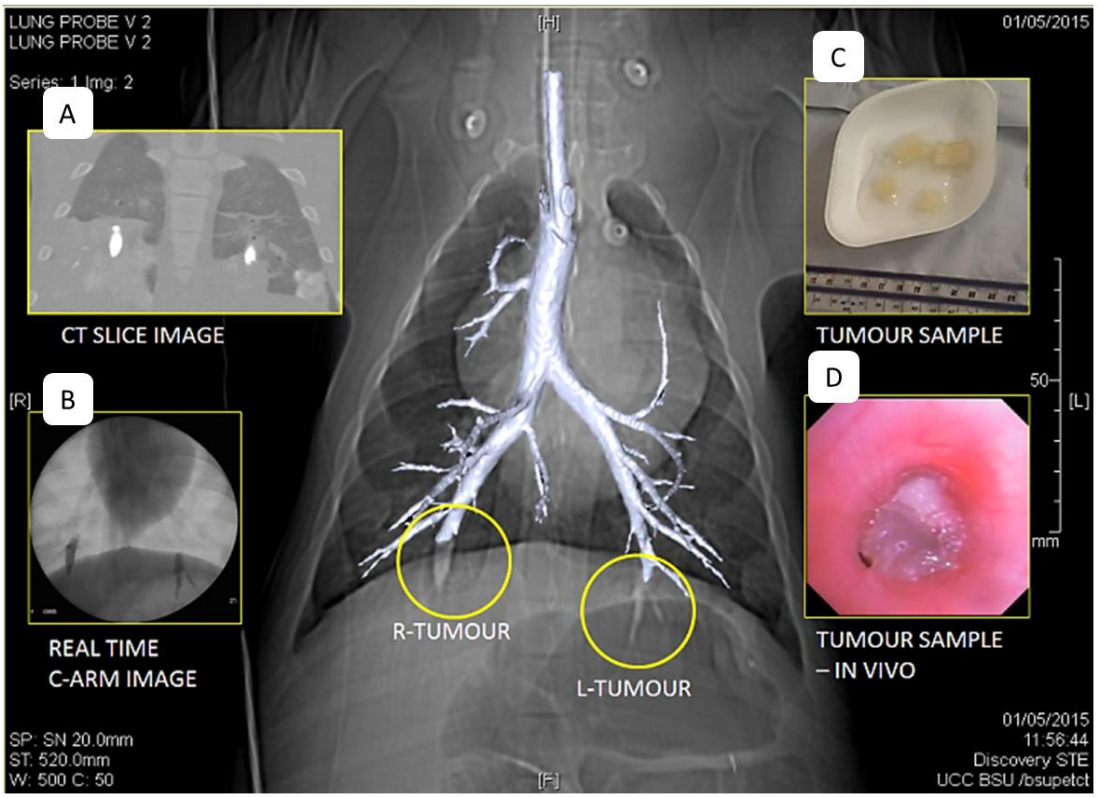


Figure 6.9. Tripe tumour models visible in lower right and left lobes (main) with overlaid images of a CT slice through the models (A), a C-arm X-ray image taken in real time while placing the models (B), and images of the tripe modes prior to insertion and positioned *in vivo* (C and D).

Once the tumours were identified in the CT image, target markers were manually selected at the locations of contrasting fiducials. Eight tripe tumour models were

inserted during the third pre-clinical trial. The locations were selected to evenly distribute the models between the upper, middle and lower airways in both the left and right lung. Figure 6.10 shows the 3D slicer reconstruction [169], [170] of the bronchial airways with selected target markers corresponding with model placement. Once the centre line was extracted and the target pathway to each fiducial was created, the mean time-to-target measured 11.2 seconds. The target markers remained in place despite delays in sampling (t+4hrs) and facilitated precise sampling at these locations under virtual bronchoscopy [169] using a biopsy forceps (Radial Jaw 4, Boston Scientific). A comparison of the performance characteristics for all the models can be seen in Table 6.3.

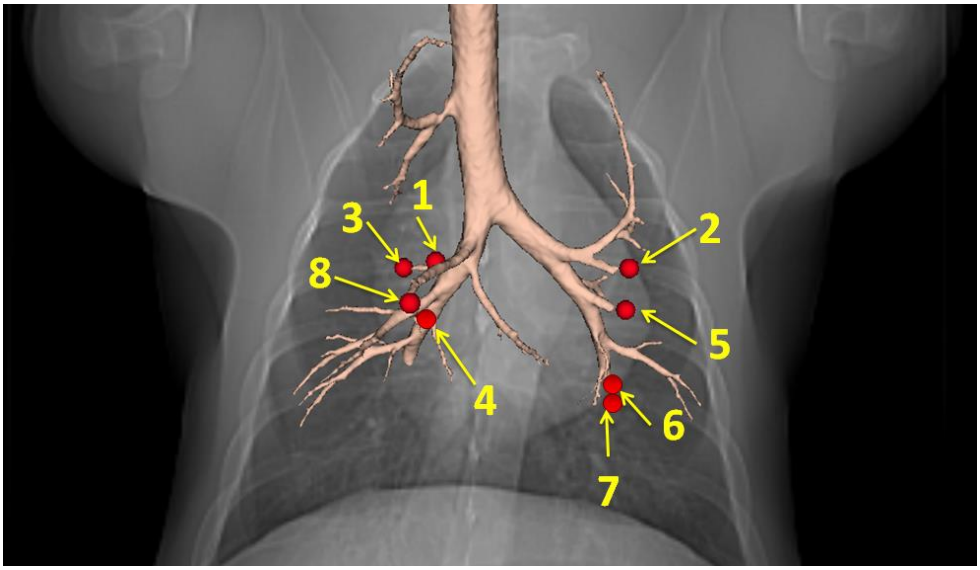


Figure 6.10. Selected target fiducials subsequent to CT scan during the third animal investigation. Areas of visible contrast resulting from tripe tumour model placement were selected by an experienced endoscopist.

6.2.5. Discussion of Tumour Model Results

The aim of this study was to develop novel soft-tissue mimicking, radiopaque tumour models and to assess their aptness in a clinically accurate physical simulation. Numerous models have been developed to mimic the characteristics of biological tissue particularly in the area of ultrasonic propagation and elastography [152], [156]–[159], [171], [172]. However, a method of combining both the physical characteristics of biological tissue and the contrasting ability of radiopaque markers in the airways has still to be fully explored. This study investigated two possible tissue mimicking radiopaque models which may be used to model pulmonary lesions.

Agarose presents key benefits as a tumour model. It forms a bulk substance when cooled providing a soft tissue-like structure. The agarose used in this analysis (type I-A:

low EEO), which was sourced from Sigma Aldrich, has a specified gel strength of >2500 g/cm^2 at 1.5% concentration. It can be introduced into the bronchial airways either endoluminally or transluminally. Model D was modified to improve injectability with an agarose concentration of 1.5%, and enhanced image contrast with the addition of Omnipaque (20%). This recipe evolved from trial and error and originating from Model A with a concentration of 7.5% proposed by Chmarra *et al*. (2014). Through experimentation it proved possible to inject Model D concentration through a 1.8 mm sheath at 40˚C. Despite seeing congealed nodules in an inflatable swine lung that resembled well formed, tumour-like models on review by clinical experts, reproducing same in a live breathing specimen is problematic. Agarose tumour placement resulted in material congealing in the lower airways. This is most likely due to material migration under continuous ventilation and prolonged liquid-to-gel transition time (t > 4 minutes). Another factor that contributed to the lengthy gel transition time is the normal core body temperature of the porcine model which can be 3°C greater than that of a humans. While this current configuration may be sufficient at 37°C in humans, it does not appear to work in the porcine model. The introduction of chilled saline helps to promote rapid congealing of the agarose material. However, this requires suction to remove excess fluid from the field of view. Alternatively, in future trials, an agarose gel, such as type VI-A with a higher gelling temperature (41 ± 1.5°C at 1.5%) may be used.

The iodine infused tripe model presents a more desirable solution as a tumour model for the *in vivo* setting. Tripe is easy and cheap to use; it can be prepared quickly, positioned rapidly within the pulmonary vessels (although not via the bronchoscope's working channel), and results in a clear image contrast under CT imagery when enriched with iodine. Tripe in itself is a biological soft tissue from the lining of a bovine stomach with similar characteristics to tumour models on visual inspection of CT images. It is easy to manipulate with endoscopic instruments and remains substantially intact despite continuous grasping and releasing with biopsy forceps. Distal airway placement is inhibited due to the requirement for forceps manipulation. The tripe sample must also be fresh and kept refrigerated to avoid deterioration and odorous build up. The sample is then brought to room temperature before insertion to reduce material stiffness on insertion. A table comparing the performance of the tripe and agarose models can be seen in Table 6.3.

Table 6.3. Summary of performance characteristics of tumour models.

	Agarose A	Agarose B	Agarose C	Agarose D	Tripe
Manufacture Time	60 minutes	60 minutes	60 minutes	60 minutes	15 minutes + Leave soak overnight
Pre-Op Preparation Time	30 minutes	30 minutes	30 minutes	30 minutes	10 minutes
Specialist Equipment Required	Yes	Yes	Yes	Yes	No
CT Visibility (Hounsfield Unit)	85±8	293±49	720±76	777±300	1707±430
Time-to-placement	2 minutes	2 minutes	2 minutes	2 minutes	2 minutes
Endobronchial Visibility	Clearly visible	Clearly visible	Clearly visible	Clearly visible	Clearly visible
Insertion temperature (Agarose only)	65˚C	60-55˚C	50-45˚C	45-38˚C	N/A
In vivo Usefulness	Was not evaluated *in vivo*	Was not evaluated *in vivo*	Low viscosity at insertion temperature facilitates easy migration to distal segments of the airway branches	More prone to migration and slower to congeal. Greater image contrast comparable with bone making model clearly visible. May also be injected transbronchially	May be inserted endobronchially with forceps and positioned easily. Sample size may be too large to reach narrow distal areas. Very high image contrast comparable with dense bone making the model easily detectable
Ex Vivo Usefulness	Requires high temperature to maintain low viscosity. Contrast similar to soft tissue therefore difficult to distinguish	Improved image contrast comparable with dense tissue observed in soft tissue explant	Viscosity modified for lower insertion temperatures. Produces well-formed fiducials when cooled	Longer shelf life with the addition on Dometriazole. Enhanced image contrast	Easy to prepare and insert. Produces well-formed radiopaque fiducials that may be biopsied.

The soft tissue explant (chicken fillet) was the first physical simulation used to assess early tumour models and provided an image contrasting comparison between the tumour model and soft tissue under CT. However the homogenous nature of a single chicken fillet lacked the complexity and intricacies of a lung. The inflatable swine lung provided a more realistic representation, one which could be controlled to simulate artificial breathing. However, the ex vivo swine lung could not accurately replicate the dynamic axial contractions encountered in a live breathing specimen. The lungs were inflated in a vacuum thus keeping the bronchus accessible to the bronchoscope, obviating the need to initiate ventilation, which in turn did not accurately reflect the clinical setting.

In addition the preserved swine lung lacks the humidity present in a live model which resulted in a misleading ease of nodule formation of the agarose model. The live porcine model presented a realistic experience of *in vivo* radiopaque tumour model placement, albeit at a higher temperature to the human model. In order to reach distal airways of the porcine lung, an adolescent specimen was used providing a shorter snout-to-bronchial distance. This in turn increased the risk of premature mortality due to infection or anaesthetic difficulty. Adolescence also increased the risk of pneumothorax and larger animals were investigated subsequently (n=3).

6.3. Chapter Review

The immediate application for these tumour models may be seen in bronchoscopic training providing a radiopaque target with similar material density properties to soft tissue. The tumour models may be deployed *ex vivo* or *in vivo* and once located under computerised tomography, the trainee may steer towards the lesion analogue before sampling the model for confirmation of localisation. The second immediate application for these models is to evaluate existing and emerging bronchoscopic imaging and navigation systems such as virtual bronchoscopy.

Both the iodine infused agarose and tripe models simulate a viable analogue of a radiopaque pulmonary lesion. The use of several different physical models aided the assessment of both agarose and tripe as tumour models. The time-to-placement and time-to-target in both the swine lung and pre-clinical investigations suggests a user friendly and quick method to create fiducials that can replicate the imaging effects of pulmonary lesions. For *ex vivo* evaluations, agarose produces well-formed injectable

fiducials as seen in the inflatable lung model. However, the iodine enriched tripe models present a more effective tumour model for *in vivo* investigations. Alternative agarose material with higher gel transition temperatures should be further investigated for the *in vivo* setting. Despite limitations, the tumour models presented in this work can be deployed endobronchially, located with CT imaging for subsequent sampling, and simulate pulmonary tumour nodules for endoscopic training and device evaluation.

6.3.1. Project Implementation within a QMS

The work described in this chapter may be retrospectively applied to a design control process. However, firstly the objective for doing so must be clearly defined. Previous Chapters looked at devices with clinical and commercial potential and focused on both the market requirements as well as the product development. Whereas projects, which are simply research orientated, may have different objectives. If the ultimate aim is to simply develop a tumour model for training purposes in *ex vivo* or simulated models for trainee endoscopists, it is therefore not defined as a medical device and is not subjected to the international medical standards and directives. However, there may still be a commercial application and if so, implementing a design control process, which maps the route for commercial feasibility and a traceable design history file, would be enormously advantageous.

If the design team wish to further progress with the artificial tumour model project to evaluation in a clinical setting, it is therefore deemed a medical device and would be bound by ISO 13485 and the MDD 93/42/EEC. The intended use in this case may be deemed as an implantable short/long term device in which case it may be classified as a Class III device with all the additional requirements that entails.

Unless a truly compelling commercial argument can be made through the development of a Market Requirement Specification and subsequent business models, it would not be feasible to pursue this project as a medical device. A more realistic proposition is to develop the models as an *ex vivo* training tool. In this case, the cost and time implications are dramatically reduced. Tractability and biocompatibility of materials, despite being still important from a production quality point of view, are not as essential. The selection of suppliers would no longer be bound to those with qualified medical device quality systems and moves more towards the consumables market which will ultimately reduce cost of goods sold. A controlled design process is still necessary to

maintain standards of production quality and post market surveillance. Development of verification and validation protocols will be essential to trouble shooting any and all design/production defects. However, ultimately the process for CE marking is much more straight forward, and once minimal risk is demonstrated by the manufacturer, he/she may prepare a Declaration of Conformity and may affix the CE marking on their own product.

Chapter 7 Summary and Future Work

"I never did anything worth doing by accident, nor did any of my inventions come by accident; they came by work." **Thomas A Edison**

An examination of user-centred medical devices has been presented in this thesis. The primary goal was to develop these projects within a controlled framework. However, each device achieved varying levels of success in realising this aim. Furthermore, this thesis presented additional research with novel outcomes and findings in the area of artificial tumour models and explores how this may fit into such a design control framework. This chapter summarises the novel contributions derived through this thesis, reflects on the implementation of design control, and highlights proposals for future work.

7.1. Proposals for Future Work

The object of this thesis was to design and develop novel devices within a controlled process to bridge the gap between traditional academic research, and industrial applicability, in medical device design. A simplified design control framework was presented (Chapter 2) and applied either retrospectively or throughout the development of three novel technologies (Chapters 3-5) derived from user-defined clinical. This thesis also presented novel research in the fields of artificial tumour modelling (Chapter 6) and discussed the merits of retrospectively applying such a project within a controlled framework.

The work presented in this thesis poses a broad scope for future work in furthering the quality control system, advancing technological device development, executing clinical evaluation and achieving commercial application. The following sections will describe in more detail the pitfalls and future requirements addressing each chapter.

7.1.1. Quality Management System (QMS)

The current QMS is established to record and control design iterations and evaluation methods. The focus is to create a development plan that considers converting real clinical needs to design specification and to organise appropriate verification and validation activities to demonstrate technical feasibility. However, as indicated in Chapter 2, within the university setting, the execution of the full design control process is unlikely. The current QMS only focuses on the document and design control activities and management responsibilities with vendor controls adopted from the university procurement policy. Therefore in order to seek ISO13485 accreditation, further development is required to capture the full range of controls of the international standard. However, accreditation is not necessarily required. For clinical study approval, documented fulfilment of the medical device directive's essential requirements within the scope of the study protocol must be presented to the national competent authority, whilst also fulfilling the requirements of the local ethics committee. A document control system which can demonstrate sufficient technical and clinical safety through certified verification and validation can successfully meet these requirements without ISO 13485 accreditation. Therefore, the proposed future work is to expand the QMS to cover all aspects of the essential requirements for pre-

CE marked devices and to execute future projects in the UCC BDRG through this quality framework.

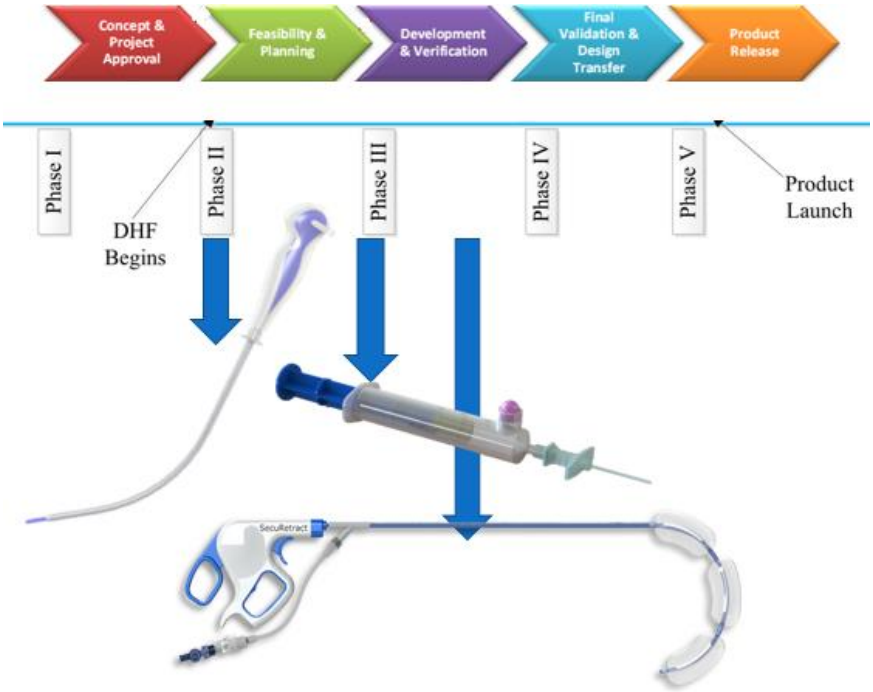


Figure 7.1 Project progress development within a control process overview.

7.1.2. SecuRetract Laparoscopic Bowel Retractor

The SecuRetract device presented in Chapter 3 proposed a number of advantages over commercially available devices which were evaluated through preliminary technical analysis, pre-clinical experimentation and end-user feedback. The SecuRetract project was developed in parallel with the development of the QMS and was therefore retrospectively applied to the design control process. Despite now in Phase III of the control process, many of the documents within the design history file are far from completion. Limited resources restrict progress in certain key areas. For a surgical invasive Class IIa device like SecuRetract, extensive biological, design and sterilisation testing is required to ensure full compliance with the regulations. However, these are often high cost specialised activities and go beyond the traditional research carried out within the University setting. The main positive from retrospectively applying the design control process was encouraging end user feedback throughout. During the initial stages of device development, predicate concept solutions were often over developed before clinical engagement resulting in wasted time on unsuccessful ideas. The design control process focusses ones attention on achieving key milestones in a most effective manner.

Further pre-clinical trials are required to validate the updated prototype design before a first-in-man clinical study may be conducted to validate clinical utility. A clinical study will also demonstrate the difference in efficacy compared to commercially available retractors, validating the clinical benefit. In order to comply with the requirements of the Irish competent authority (HPRA) to undertake a clinical study, the following proposed future works are required:

- Compile a Design History File to satisfy the needs of ISO 13485 Section 7.
- Finalise risk analysis in accordance with ISO 14971.
- Carry out sterilisation verification (e.g. utilising biological indicators on an ethylene oxide sterilization cycle).
- Carry out design verification on sterilised sample units (protocols to satisfy prerequisites from risk and regulatory requirements).
- Bio-compatibility testing (through equivalence to commercially available materials and technology if possible).

It is not envisioned that shelf-life testing, transportation testing, or process validation is required within the scope of the pre-CE clinical study. These works will be carried out on a verification batch manufacture, fabricated by a qualified supplier, and co-ordinated via a spin-out entity from University College Cork to champion the commercial opportunity of SecuRetract.

7.1.3. ProDural Epidural Syringe

The work presented in Chapter 4 describes the design and development of an epidural location device which has the potential to reduce the incidence of dural punctures, to reduce the rate of false positive applications, and to reduce the steep learning curve associated with epidural administration. The resulting device, ProDural, retains the loss-of-resistance technique preferred by anaesthetists, whilst providing an additional visual indication that the epidural space has been reached. The ProDural project has achieved the key objectives associated with Phase II of the design control process and future work will focus on optimising the design for manufacture and to fulfil the stage gate objectives of Phase III and IV to enable clinical validation. Capital investment is required to design the tooling and moulds required to blow a custom syringe and to validate finalised production processes for a

minimally viable product. This presents opportunities to partner with multinational, mass volume corporations and to explore business licencing prospects.

Clinical studies are required to validate the clinical utility. This will require the determination of the size and cost of any future clinical studies with a sufficient confidence level to show the clinical efficacy of ProDural in improving procedural outcomes. Further due diligence is required to fully assess the intellectual landscape and to add sufficient novelty to secure patent protection. This may involve further design refinement. The minimum achievable cost of goods sold (COGS) at scale should be determined to calculate a reasonable price premium which could be absorbed by the payers, while still ensuring a customer cost saving. These activities will require additional resources which may be supported by non-venture capital sources of funding to advance the project needs (industry partnerships, migraine headache/patient interest groups, etc.).

7.1.4. SafeTrac Intubation Device

The SafeTrac device presented in Chapter 5 represents an exciting commercial opportunity in the vast intubation market. Globally, there are more than 65 million annual intubations performed and the current prototype may offer a cost-effective, steerable option to improve intubation. SafeTrac is the only device to have been developed from the beginning within a design control process. However, the project has only just begun to execute the tasks as part of Phase II of the control process. Further time is required to continue its development within the QMS which will provide the first true evaluation of the presented design process.

Despite a promising preliminary assessment of a functional concept prototype, additional design and development is required to add significant novelty to secure patent protection and to enhance the value proposition. Further design iteration exploring different materials and geometries is required with continuous feedback from clinicians. Optimising the design to reduce the cost of manufacture is critical to the application of ETT placement. However, end-user surveys have identified several potential beneficial enhancements that may include CO_2 sensors to detect inadvertent placement in the oesophagus, which may justify a higher cost point. The SafeTrac project presents the broadest scope of development and is ideally placed to attract government support and researchers to further develop the technical and commercial potential. This low risk

device employees simple technology and can significantly benefit from further design development and analysis.

7.1.5. Radiopaque Pulmonary Tumour Model

The tumour models presented in Chapter 6 were initially developed to provide artificial lesions to evaluate an emerging bronchoscopic imaging and navigation system being developed at the Biomedical Design Research Group at UCC. The tumour models were developed to evaluate this new system during pre-clinical animal investigations and provided detectible and retrievable markers. The iodine-infused agarose model and tripe model may also have immediate application in bronchoscopic training, providing a radiopaque tissue-like target. The tumour models may be deployed *ex vivo* or *in vivo* and once located using CT-imaging, the trainee may steer towards the lesion analogue before sampling the model for confirmation of localisation. However, further refinement of the agarose model is required to promote rapid congealing at body temperature and improve ease of injection through lower gauge aspiration needles (21 / 22 gauge). This may involve selecting different types of agarose samples with higher gelling temperatures. In addition, further mechanical analysis will need to be carried out to compare the stiffness and bulk density of the congealed agarose gel to actual malignant growths.

The tripe model provides a cost effective and easy to prepare soft-tissue model. It was noted during experimentation that despite extended soakage time in a high contrast medium, the tripe did not effectively absorb the iodine contrast and required further injection prior to application. Therefore, alternative means of infusing the tripe to improve initial absorption and subsequent retention of the contrast medium should be investigated. In addition, further analysis is required to characterise the physical mechanical properties of the tripe sample and to compare same with soft tissue.

Initially there was no intention of developing the tumour project within a design control process as the primary object was to create an effective fiducial to target under CT imaging. However, during the development of this project, the novelty and application of such models to aid in bronchoscopy training become increasingly evident. Therefore, this project was included as part of this thesis to promote discussion as to how such a research project may be retrospectively applied to a design control process. Implantable devices such as the agarose and tripe tumour model, if

intended for use in human beings, with qualify as a Class III medical device. Class III device require extensively more testing and verification to gain approval and have much more complicated and lengthy approval processes (e.g. PMA in the USA). Therefore, the author would advise that should this project be pursued further, the purpose should be to develop artificial radiopaque models for ex vivo training only. In this instance, the design control process may be applied whilst ignoring certain requirements such as sterility and biocompatibility, reducing the overall cost and project lead times, and still ensuring quality product development. This also presents the opportunity of partnering with anatomical training companies such as CAE Healthcare (Blue Phantom).

7.2. Thesis Conclusions and Final Remarks

This objective of this PhD thesis was to develop novel, user-cantered medical devices within a design control framework. Despite identifying and developing novel technologies with commercial application, the author did not achieve full execution of any project within the defined procedures of the QMS. It is the hope of the author that the basis of the QMS which was developed will be expanded upon and refined to allow it to be flexible as well as compliant with the international design control requirements. Furthermore, it is a goal that ultimately such a system may be exported internationally to aid in compliant medical device development, not just for hardware devices, but also for software.

The principal advantage of implementing a QMS and design control process, besides being an absolute requirement for clinical implementation, is that it focuses the design team with a step wise approach to product development with clear defined objectives at each phase. The complete process not only prescribes the development from a technical point of view, but also identifies the clinical, performance, user and market requirements that should feed into deriving the design inputs and specifications. The current milestones at each phase were modified from those presented in literature to meet the author's experience, particularly during the very early stage of expository work. As the system is tested through future product development, it may be amended though simple change controls to account for the growing team's needs.

The major disadvantage and criticism, experienced by the author, is that the development, implantation and execution of a quality management system and product development is perhaps too much for one person or small teams. It is vital that once fully

up and running, the responsibility for executing and maintaining is appropriately distributed but also controlled by the single final approval of the principal investigator on all major reviews. Where possible, software based project management and automatic scheduling can relieve the burden of paperwork, and certified e-signature applications such as Adobe Acrobat Pro can expedite approval processes. Furthermore, procedural training may be achieved by employing online training programs such as Moodle and protected cloud storage may be used for document archiving and retrieval. One designated quality assurance manager will still be required to ensure compliance across a research group and centre. However, a flexible, efficient system can only aid in a research's design and development process and should be embraced in the academic setting.

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Appendix 1 – Quality Manual

(Uncontrolled Sample)

QUALITY MANUAL

Document No.: BDRG-QM

Revision No.: [UNCONTROLLED SAMPLE]

BIOMEDICAL DESIGN RESEARCH GROUP

BDRG QUALITY MANUAL (SAMPLE)

Approvals

The signatures below certify that this document has been reviewed and accepted, and demonstrates that the signatories are aware of all the requirements contained herein and are committed to ensuring their provision.

	Name	Signature	Position	Date
Reviewed by			[insert position]	
Approved by			[insert position]	

1. Introduction and Scope

1.1 General

The Quality Manual of the Biomedical Design Research Group (BDRG) at University College Cork's (UCC) School of Engineering is compiled in accordance with EN ISO 13485 (Medical Devices – Quality management system requirements – Requirements for regulatory purposes ISO 13485:2003).

The purpose of this document is to define and communicate the processes established for the effective monitoring and operation of the BDRG quality management system.

The quality management system is designed to provide a framework for medical device design that meets regulatory and end user requirements. This manual also outlines the methods by which the BDRG maintains the effectiveness of the quality management system in line with the applicable quality and regulatory standards.

1.2 Scope and Application

The BDRG design and develop devices for clinical use. This document covers the design, prototyping and evaluation of medical devices conceived within the BDRG. All medical devices developed by the BDRG are intended for clinical investigation and/or future commercial approval.

The BDRG are not claiming any exclusions from ISO 13485. However some non-applicable clauses have been identified due to the nature of our activities:

- The BDRG does not provide installation or servicing for customers. The installation and servicing requirements of Sections 7.5.1.2.2 installation activities and 7.5.1.2.3 servicing activities are not applicable.
- The BDRG does not manufacture or supply implantable or active implantable devices, therefore the following clause are not applicable;
    - 8.2.4.2 Particular requirements for implantable medical devices
    - 7.5.3.2.2 Particular requirements for active implantable medical devices and implantable medical devices
- The BDRG does not 'place devices on the market' or distribute commercialised medical devices. The post market surveillance requirements are therefore excluded from this quality management system (QMS).

1.3 Organisational Profile

The Biomedical Design Research Group (BDRG) is a core research group in the School of Engineering at University College Cork. The group's primary purpose is to identify and solve unmet clinical needs through user-centered design in keeping with best industrial practices for the development of medical devices.

1.4 Organisational Structure

The Biomedical Design Research Group adheres to UCC's corporate procurement and health and safety policies and solely carries out developmental research and clinical evaluation. Clinical product manufacturing, packaging and sterilisation are outsourced to regulated suppliers. Working closely with the UCC Technology Transfer Office, the intellectual property surrounding each of the devices will be defined and, where appropriate, protected by patent applications.

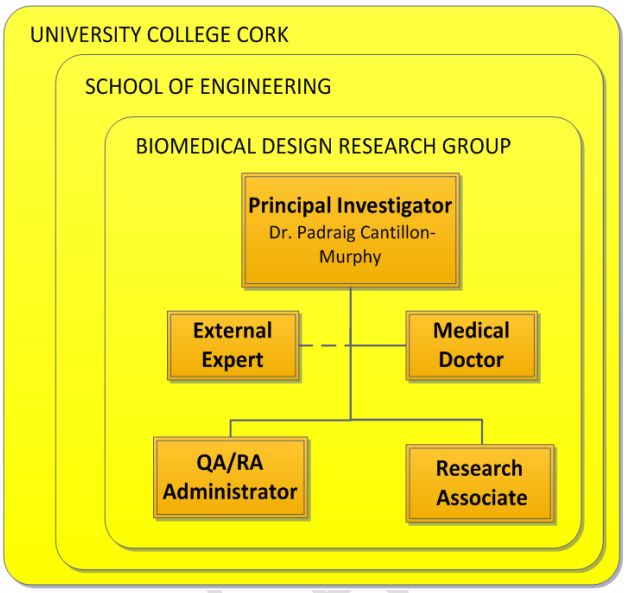

Figure 1 BDRG organisational structure

The organisational structure and the roles and responsibilities of individual functions apply to each project undertaken by the BDRG and are transferable to newly appointed research personnel. An organogram of the BDRG's organisational structure can be seen Figure 1.

1.5 Biomedical Design Research Group Quality Policy

Every member of the group is responsible for the quality of his or her own work. The group is committed to designing and developing high quality products that are safe and effective and which meet or exceed users' needs and expectations. The group will achieve this commitment by;

- Understanding and meeting the needs of end-users through research, design and testing.
- Complying with applicable national and international regulations.
- Maintaining and continuously improving the effectiveness of the quality management system.

2. References

Reference	Title & Description
EN ISO 13485:2012	Quality management systems for medical devices
EN ISO 14971:2012	Application of risk management to medical devices
MDD 93/42/EEC	Medical Device Directive of the European Union as it applies to the Quality Management System

Note: See Appendix 4 for referenced procedures

3. Definitions and Abbreviations

Term	Definition
Medical Device	Any instrument, apparatus, implement, machine, appliance, implant, in vitro reagent or calibrator, software, material or other similar or related article, intended by the manufacturer to be used, alone or in combination, for human beings for one or more of the specific purpose(s) of • diagnosis, prevention, monitoring, treatment or alleviation of disease, • diagnosis, monitoring, treatment, alleviation of or compensation for an injury, • investigation, replacement, modification, or support of the anatomy or of a physiological process, • supporting or sustaining life, • control of conception, • disinfection of medical devices, • providing information for medical purposes by means of in vitro examination of specimens derived from the human body, and which does not achieve its primary intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means.
Implantable medical device	Medical device intended • to be totally or partially introduced into the human body or a natural orifice, or • to replace an epithelial surface or the surface of the eye, by surgical intervention, and which is intended to remain after the procedure for at least 30 days, and which can only be removed by medical or surgical intervention.
Active medical device	Medical device, operation of which depends on a source of electrical energy or any source of power other than that directly generated by the human body or gravity and which acts by converting this energy.
Risk	Combination of the probability of occurrence of harm and the severity of that harm.
Clinical evaluation	Assessment and analysis of clinical evidence pertaining to a medical device to verify the clinical safety and performance of the device when used as intended by the manufacturer.
Complaint	Written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety or performance of a medical device that has been released from the organisation's control.

Distributor	Any natural or legal person in the supply chain who, on his/her own behalf, furthers the availability of a medical device to the end user.
Advisory notice	Notice issued by the organisation, subsequent to delivery of the medical device, to provide supplementary information and/or to advise what action should be taken in • the use of a medical device, • the modification of a medical device, • the return of the medical device to the organisation that supplied it, or • the destruction of a medical device.
Importer	Any natural or legal person with responsibility to first make a medical device manufactured in one jurisdiction available in another specified jurisdiction.
Labelling	Written, printed, graphic or electronic information • affixed to a medical device or any of its containers or wrappers, or • accompanying a medical device, • provided for a medical device by other means Related to identification, technical description, intended purpose and proper use of the medical device, but excluding shipping documents.
Life-cycle	All phases in the life of a medical device, from the initial conception to final decommissioning and disposal.
Manufacturer	Any natural or legal person with responsibility for design and/or manufacture of a medical device with the intention of making the medical device available for use, under their name; whether or not such a medical device is designed and/or manufactured by that person or on their behalf by another person(s).
Post market surveillance	Systematic process to collect and analyse experience gained from medical devices in the post-production phase.

4. Quality Management System

4.1 General Requirements

4.1.1 System Scope

The quality management system is established to implement the requirements of ISO 13485:2012 and European Directives MDD 93/42/EEC, and to establish policies and procedures that support the objectives of the research group.

4.1.2 System Structure

This quality manual provides policy and other top-level guidance (Level I), and makes reference to standard operating procedures (SOPs) for detailed procedures on the operation of the system (Level II). Detailed procedures for supporting activities are found in Appendices, Forms, Records and other Level III documents. The sequence and interaction of processes needed for the quality system is outlined in *Appendix 3 BDRG Process Flow Chart*. Quality system documentation also defines criteria and methods needed to ensure that the operation and control of quality system processes are effective. This includes assignment of responsibilities and allocation of resources for the process, instructions on how to carry out and operate the process, definition of methods for monitoring, measuring, and analysing the processes and actions necessary to achieve planned results and continually improve the processes. The PI is responsible for determining resources and information requirements necessary to support the operation and monitoring of quality system processes.

4.1.3 System Processes

The Principal Investigator approves initial release and changes to this document through the change control request (CCR) process.

Internal audits are used to evaluate the effectiveness of the quality system and drive improvement by monitoring and measuring the outcome of these processes. Management review also ensures availability of adequate resources and technology to support the QMS. The monitoring of process objectives is outlined in *F 5.6-01 Key Process Metrics*.

Where processes are outsourced, the BDRG complies with UCC's procurement policy. Additional criteria to meet the requirements of ISO 13485 are enacted for processes and material intended for clinical use as outlined in SOP 7.4 Purchasing and Vendor Management Procedure.

4.1.4 Clinical Evaluations

The scope of the quality system covers the design and development of medical products for clinical research and eventual commercialisation.

Clinical evaluation activities are also covered as follows:

- Any clinical investigations conducted utilising investigational medical devices will be conducted in accordance with ISO14155 clinical investigation of medical devices for human subjects – good clinical practice.
- Roles and responsibilities for any clinical investigations will be defined in an approved study specific clinical management plan.

- Identifying the processes and documentation required for the clinical evaluation in support of the technical activities and applying these processes.
- Ensuring that the processes used and the control of these processes is efficient and effective.
- Monitoring, control and analysis of the processes on an ongoing basis.

Procedures Relating to Clause 4.1 Quality System	
SOP 7.4	Purchasing and Vendor Management Procedure
SOP 5.6	Management Responsibility Procedure

4.2 Documentation Requirements

4.2.1 General

A quality management system based on the specific requirements of ISO13485 and incorporating additional end user requirements has been implemented by the BDRG. The documented quality management system shall include the following:

(a) Documented statement of a quality policy and quality objectives (see Appendix 1);

(b) A quality manual is reviewed as required and approved by the PI and QA/RA Administrator through the change control process;

(c) Quality procedures shall be documented and implemented for each activity undertaken by the research group to ensure a consistent and systematic approach in product design and development;

(d) Documents needed to ensure the effective planning, operation and control of its processes;

(e) Quality records to demonstrate compliance to our documented quality management system, and user requirements;

(f) Any other documentation specified by national or regional regulations.

The documented quality management system in operation in the BDRG is structured into three levels as follows;

Level 1: The Quality Manual;

- The quality manual is the top level document that describes the overall quality system in accordance with the stated quality policy and ISO 13485:2012.

Level 2: Procedures;

- The standard operating procedures establish the research groups' practices, procedures, policies and requirements. They are drafted from both a technical and clinical perspective and use a general format, with flow charts and diagrams as applicable. The quality manual references the applicable SOP(s). Standard operating procedure numbers are assigned according to the corresponding ISO 13485 Clause. E.g.

SOP 4.2 is the procedure for Document Control Procedure (ISO 13485 clause 4.2). Level 2 records also include product specifications, drawings and process specifications.

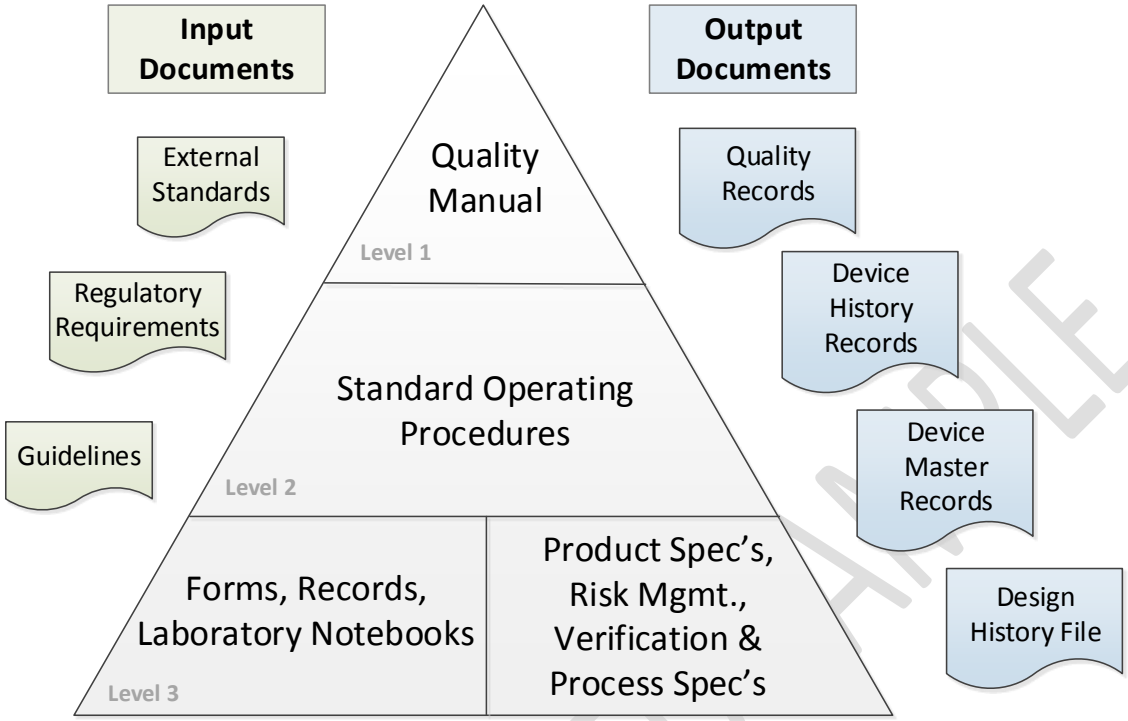

Figure 2 QMS Structure

Level 3: Forms, Records and Specifications;

- The third level of documentation includes Forms and Records which provide evidence about a past event stating results or activities performed.
- Laboratory Notebooks record the design and development activities of the research associate.
- Product Specifications define product characteristics, including functional characteristics, risk management, validation and verification, packaging and sterilization processes, and manufacturing processes.

The **Design History File** (DHF) contains design and development history for the device, such as product requirements, design and development plan, FMEA/risk management, quality plan, design change records, validation documents etc. These are all examples of level 3 documentation.

4.2.2 Quality Manual

The Quality Manual (this document) defines the policies, application, scope, exclusions and documentation of the quality management system. The quality manual includes;

- The scope of the quality management system, and details of and justification for any exclusion.
- Reference to documented procedures established for the quality system which clearly show the relationship between the requirements of the standard and documented procedures.
- A process map that clearly identifies the description and interaction between the processes of the quality management system (see Appendix 3).

4.2.3 Control of Documents

A documented procedure is in place ensuring that documents defining products, processes, and the quality system are approved before controlled release and distribution. This is achieved electronically via a shared cloud network which has restricted access to project personnel only. A master document list is maintained with the latest revision of each document in the quality management system. Different rights and permissions are associated with each member of the project team and the overall management and maintenance of the shared network is the responsibility of the QA/RA Administrator or designee. Obsolete documents are removed from the master document list and are stored in an obsolete folder. These documents are only accessible to the QA/RA Administrator and PI or designee. External documents such as industry or agency standards are controlled in the same way as internally generated documents. The QA/RA Administrator is responsible for document control. However, all personnel are responsible for using the correct documents, at the prescribed revision level, at all times.

SOP 4.2 Document Control and SOP 4.2.3 Change Control Procedure details the following requirements:

(a) Review and approve documents for adequacy prior to issue;

(b) Review and update as necessary and re-approve documents;

(c) Ensure that the changes and the current revision status of documents are identified;

(d) Ensure that relevant versions of applicable documents are available;

(e) Ensure that documents remain legible & readily identifiable;

(f) Prevent unintended use of obsolete documents and to apply suitable identification to them if they are retained for any purpose.

A review of all Standard Operating Procedures shall be completed on an annual basis to ensure that the contents are current and valid. For external documents an annual review is also conducted to ensure document revisions are current.

4.2.4 Approval and Issue

Documents are approved by the individual's assigned responsibility for the particular document. Once a document has been approved it is uploaded to the shared cloud network by the QA/RA Administrator and filed in the master document folder.

Documents are maintained on the shared network as read only in the document control system. If a document or process requires a change/amendment during the course of the project, it should follow the Change Control Process as outlined in SOP 4.2.3 Change Control Procedure. A Master Change Control Log is maintained for all changes.

4.2.5 Control of Records

The BDRG establishes and maintains quality records to provide evidence of conformance and the effective operation of our documented quality management system and the end user's specific requirements. Quality records shall be legible, readily identifiable and retrievable. Records are identified, indexed and grouped to facilitate their retrieval.

4.2.6 Retention

Retention periods for quality records are determined on the basis of the event to which the record pertains, and on regulatory and contractual requirements as applicable. Retention times of quality records, and disposition requirements, shall be referenced in SOP 4.2 Document Control Procedure.

Procedures Relating to Clause 4.2 Documentation Requirements	
SOP 5.6	Management Responsibility Procedure
SOP 4.2	Document Control Procedure
SOP 4.2.3	Change Control Procedure

5. Management Responsibility

5.1 Management Commitment

The BDRG is committed to implementing, and maintaining a documented quality system. This commitment includes: ensuring that user, regulatory and legal requirements are understood and appropriately addressed, the quality policy is understood and implemented at all levels of the group, quality objectives and plans are established as necessary and that the responsibilities of all functions affecting quality are clearly defined. The Principal Investigator is responsible for establishing, implementing, and continuously improving the quality system. Personnel and other necessary resources are provided to accomplish the goals of the quality system.

There are several processes by which the Principal Investigators communicate to the rest of the research group regarding user, regulatory and legal requirements and the importance of meeting these requirements.

- Informational meetings and project meetings are conducted periodically.
- Training is conducted on a regular basis according to the requirements specified in the training SOP and this training is documented and includes training to regulations, etc.
- New employees go through a series of training, so they have a thorough understanding of the research group as well as clinical and regulatory requirements.

Management Reviews and internal audits are conducted periodically to ensure that the quality system is effective. Management review is the mechanism by which opportunities to improve are identified and resources are allocated to achieve those improvements. Quality objectives are defined at these reviews.

Procedures Relating to Clause 5.1 Management Commitment	
SOP 5.6	Management Responsibility Procedure

5.2 User Centered Design

The BDRG shall ensure that user needs and requirements are identified to allow for design solutions which meet user requirements as well as applicable regulatory requirements. User needs, including other applicable requirements, will generally be identified by way of structured

academic programs (e.g. Bioinnovate, UCC BioDesign), direct clinical engagement & technology partners. User requirements are determined, converted into internal requirements, and communicated to the appropriate people in the organisation.

Procedures Relating to Clause 5.2 Customer Focus	
SOP 7.3A	Design Control Procedure

5.3 Quality Policy

The BDRG has documented a quality policy. Management ensures that the quality policy is;

- Appropriate to the purpose of the group;
- Reflects the organisation's quality objectives and the framework for setting and reviewing same;
- Outlines the commitment to comply with requirements and to maintain the effectiveness of the quality management system;
- Communicated and understood within the group.

The quality policy shall be communicated to all group personnel by posting in the group office areas. The quality policy shall also be communicated and explained during induction and personnel understanding of the policy by personnel shall be examined. The policy shall be reviewed and updated as appropriate during the management review meeting in order to ensure the policy's continuing suitability for the group. Refer to Appendix 1 for the current Quality Policy.

Procedures Relating to Clause 5.3 Quality Policy	
SOP 5.6	Management Responsibility Procedure

5.4 Quality Management System Planning

The planning for the quality management system is carried out by the Principal Investigator and project leads during management review meetings where quality objectives are set and reviewed. Quality planning includes identification and determination of quality system processes, priorities for continual improvement, and resources needed to achieve quality objectives and to maintain and improve the quality system. When a change is made to the quality system as a result of an internal audit or management decision, it is reviewed for effectiveness and appropriate justification and approvals are required to implement the change. This change is documented as indicated in the change control process as outlined in the Change Control SOP 4.2.3.

Procedures Relating to Clause 5.4 Quality Planning	
SOP 4.2	Document Control
SOP 5.6	Management Responsibility
SOP 7.5	Control of Outsourced Manufacturing

SOP 6.2	Training Procedure
SOP 7.3A	Design Control
SOP 7.4	Purchasing and Vendor Management
SOP 8.2.2	Internal Auditing

5.5 Responsibility, Authority and Communication

5.5.1 Responsibility and Authority

Approved organograms are maintained by the QA/RA Administrator electronically. Some individuals within the group perform multiple roles. However, the roles and responsibilities relating to quality are clearly defined in later sections of this manual, in job descriptions, and in SOP's. Independence and authority necessary to manage, perform, and assess tasks affecting quality is maintained by the Principal Investigator. Job descriptions are assigned by the Principal Investigator.

5.5.2 Roles, Responsibilities & Competencies

Management Team

The management team (comprising of at least the PI (Principal Investigator), the Research Associate (Res) and the Quality Assurance and Regulatory Affairs (QA/RA) Administrator) is responsible for the leadership and direction of the group. The management team is also responsible for establishing the Quality Policy, and reviewing it for continuing suitability.

Principal Investigator (PI)

- Establish and support the quality policy by providing the necessary resources.
- Establish quality goals and objectives for the group.
- Participate in management reviews.
- Review and approve new and revised quality and product documentation.

Research Associate (Res)

- Coordinate functional and other technical requirements with users or the Principal Investigator.
- Design and initiate specification documentation for medical devices.
- Review and approve product and supporting documents for initial release and changes.
- Coordinate design control activities on assigned products.
- Initiate required documents for prototype or developmental products.
- Support ongoing device improvements, through capability and quality improvement activities.
- Initiate and review SOPs and supporting documents.
- Coordinate and when applicable carry out validation and verification of medical devices.
- Maintain positive identification and traceability of all products.

Quality Assurance and Regulatory Affairs Administrator (QA/RA)

- Coordinate and manage the group's quality assurance and regulatory issues.
- Establishing and maintaining the quality system.
- Ensuring that processes needed for the quality management system are established implemented and maintained according to the requirements of ISO 13485.
- Regular reporting on the performance of the quality system to the management team, using the information in these reports to initiate continuous improvement actions on the processes and systems used by the organisation.
- Arranging biannual management review meetings.
- Liaising with customers and third party auditors in matters relating to the quality system.
- Promoting awareness of customer and regulatory requirements throughout the organisation.
- Initiate and monitor corrective/preventive actions (CAPA).
- Coordinate internal audits and associated corrective actions (CA).
- Prepare certifications and other required quality documentation in support of device release.

Management Representative

The Quality Assurance and Regulatory Affairs Administrator (QA/RA) is the management representative for the BDRG and has the following responsibility and authority:

- Acting as Principal Investigator's agent in establishing, implementing, maintaining, the effectiveness of and improving the quality system;
- Reporting the performance of the quality system and any need for improvement to the Principal Investigator;
- Serving as the group's liaison with users and other external parties on matters related to product quality and reliability.

Contract Manufacturer

The BDRG will contract the services of a contract manufacturer to manage the manufacture, packaging and sterilisation of their products. The specific role of the contract manufacturer is outlined SOP 7.4.

Individual Roles

Refer to the individual Job Descriptions which outlines the key responsibilities and authorities for each person in the group.

5.5.3 Internal Communication

- On a periodic basis, the Principal Investigator will disseminate information regarding the project status. This will generally take place in the context of regular group meetings.
- Methods of communicating the effectiveness of the QMS include management review, circulation of minutes of management review meetings and internal audit meeting minutes.

Procedures Relating to Clause 5.5 Responsibility, Authority and Communication	
SOP 5.5	Regulatory Audits Procedure
SOP 5.6	Management Responsibility Procedure

5.6 Management Review

5.6.1 General

The principal investigator and the QA/RA Administrator formally review the quality system for compliance and effectiveness on an annual basis. The QA/RA Administrator (or designee) is responsible for calling and facilitating the review and minutes. Management Review Meeting minutes are prepared and circulated by the QA/RA Administrator (or designee) as required to provide pertinent information regarding the quality of the medical device or the effectiveness of the quality management system.

The results of the management review shall be communicated to all relevant group personnel and the progress of actions shall be examined prior to the next review. SOP 5.6 Management Responsibility Procedure has been established to outline the management review process at the BDRG. This procedure includes the required inputs and outputs of the management review meeting.

5.6.2 Review Input

The management team selects inputs to the management review process to evaluate efficiency as well as effectiveness of the quality management system. The review inputs may include quality metrics, user feedback, audit results both internal and external if applicable and corrective and preventive action. Other inputs may be added as deemed appropriate:

- Follow–up actions from previous management reviews.
- Review suitability of the quality policy.
- Results of audits (internal and external).
- End user feedback.
- Progress of the quality objectives.
- Process performance: Key Process Metrics (F 5.6-01).
- Design and development opportunities and issues.
- Types, numbers and status of non-conformities, corrective and preventive actions.
- Continued suitability of the QMS and any changes that could affect the quality management system.
- Recommendations/suggestions for improvement.
- Training requirements/plans.
- Supplier/subcontractor performance.
- Any other business.

5.6.3 Review Output

All actions arising out of the management review meeting shall be recorded, responsibility assigned and completion dates decided. The management representative shall ensure that actions are completed in a timely basis.

Management review outputs shall include:

(a) Improvements needed to maintain the effectiveness of the quality management system,

(b) Improvement to the device relating to end user requirements,

(c) Resource requirements.

The output shall include a statement regarding the effectiveness of the quality management system and its processes established for the achievement of the quality policy and the objectives, and the extent to which those objectives have been met based on the established respective criteria.

Procedures Relating to Clause 5.6 Management Review	
SOP 5.6	Management Responsibility Procedure

6. Resource Management

6.1 Provision of Resources

6.1.1 General

The Principal Investigator determines and provides the resources necessary for the implementation, maintenance, and continual improvement of the entire quality system. The Principal Investigator assigns appropriate resources to enhance user satisfaction through meeting user and regulatory requirements. Resources include personnel, infrastructure, work environment, process equipment, materials, information, suppliers and financial resources.

6.1.1 Resource Determination

The Principal Investigator determines appropriate resource needs during periodic project reviews and during management review meetings. Resource needs are established through consideration of end-user feedback and quality management improvements. The Principal Investigator considers all the resources necessary to accomplish these needs, including personnel assignments, allocation of space or equipment, training, procurement decisions, budgets, etc.

Procedures Relating to Clause 6.1 Provision of Resources	
SOP 6.2	Training Procedure
SOP 5.6	Management Responsibility

6.2 Human Resources

6.2.1 General

The BDRG shall ensure that personnel performing work affecting quality of the product shall be competent on the basis of appropriate education, training, skills and experience. The QA/RA Administrator is responsible for the training and awareness programs for group personnel, such as general orientation, rules and regulations, quality system, safety, and other group systems and issues.

6.2.2 Qualification Documentation

Written job descriptions are in place for all activities affecting product quality in order to document the qualifications and duties of the positions determined to be necessary by the Principal Investigator.

6.2.3 Assignment of Resources

Resources are assigned based on experience, education, skills and training to appropriate tasks to meet established project and quality objectives.

6.2.4 Competence

The PI will assess the competency of all group personnel on an on-going basis by way of informal weekly updates and assessing the quality of completed tasks/activities. In the case where personnel are not performing satisfactorily, corrective measures including increased supervision, assigning direct and focused objectives and additional training may be used.

6.2.5 Awareness

The PI and QA/RA Administrator complete a training plan for each personnel which determines his/her training requirements (F6.2-03 Training Plan).

6.2.6 Training

SOP 6.2 Training Procedure has been established to provide training for all personnel performing activities affecting quality and ensuring that end user and regulatory requirements are met. Training needs are assessed on inducting new personnel to the BDRG. The training needs are updated as required by the PI and QA/RA Administrator. Qualifications are reviewed prior to joining the group. All personnel are made aware of the relevance and importance of their activities and how they contribute to the achievement of the quality objectives. Training records shall be maintained for all internal and external training performed. Training on all quality documents is carried out using the online learning platform Moodle and is described in SOP 6.2 Training Procedure.

Where training is carried out, whether internal or external, the BDRG shall evaluate the effectiveness of the training. Training effectiveness can be evaluated by surveying the employee, evaluating the work performance of the trained individual, internal audits or assessment post-training delivery. Training effectiveness is reviewed at Management Review.

Procedures Relating to Clause 6.2 Human Resources	
SOP 6.2	Training Procedure
SOP 6.2.2	Moodle Instruction Manual

6.3 Infrastructure

6.3.1 General

Management is responsible for identifying the need and requirements for new and/or modification of existing infrastructure and facilities. Building and facilities maintenance is carried out by the UCC Buildings and Estates Department. The BDRG is subject to the health and safety policies of the UCC Health and Safety office.

University College Cork provides and maintains the overall infrastructure. This includes buildings, workspace and associated utilities.

The funding allocated or obtained for each project finances the equipment, tools, computer systems, etc. for each project. IT Systems are maintained and upgraded as required by the School of Engineering IT Administrator.

6.3.2 Plant, Facility & Equipment Management

The BDRG shall maintain the premises in a state of order, cleanliness and repair appropriate to the work being carried out. SOP 6.3 Calibration and Equipment Maintenance outlines the controls around equipment calibration and maintenance.

6.3.3 Outsourced Services

Manufacturing packaging and sterilisation is outsourced to suitably qualified subcontractors – reference SOP 7.4 Purchasing and Vendor Management Procedure and SOP 7.5 Control of Outsourced Manufacturing Procedure.

Procedures Relating to Clause 6.3 Infrastructure	
SOP 4.2	Document Control
SOP 7.4	Purchasing and Vendor Management Procedure
SOP 7.5	Control of Outsourced Manufacturing
SOP 6.3	Calibration and Equipment Maintenance

6.4 Work Environment

6.4.1 General

UCC provides the necessary resources for a safe and suitable work environment. The university also manages the health & safety of the work environment by utilising safety systems of work. The Human Resources office of UCC has overall responsibility for employee welfare, including university induction training, fire safety management, and routine facility maintenance. UCC maintains a health and safety policy and a comprehensive safety statement. Equipment and work environment needs are addressed through the PI.

The BDRG outsources the manufacturing, packaging and sterilisation activities. Therefore no raw materials, processing material, sub-assemblies or final product intended for human use is handled at UCC. Materials for research activities are handled in the laboratory. Control of subcontracted activities is detailed under SOP 7.5 Control of Outsourced Manufacturing.

Procedures Relating to Clause 6.4 Work Environment	
SOP 7.5	Control of Outsourced Manufacturing.

7.0 Product Realisation

7.1 Planning of Product Realisation

The BDRG plans and develops the processes needed for product realisation. These processes include the steps necessary to design and develop new devices, as well as the implementation of procedures and controlled records to detail the processes used to create and inspect the devices. In planning product realisation, management determines and documents the following, as appropriate:

- Quality objectives and requirements for the device, in particular, regulatory requirements for the various regions that the device may be sold in.
- Identification of end user requirements.
- The need to establish processes, documents, and provide resources specific to the device.
- Risk management planning and reporting.
- Required verification, validation, monitoring, inspection, and test activities specific to the device and the criteria for device acceptance.
- Records needed to provide evidence that the realisation processes and resulting device fulfil requirements.

Management has established appropriate risk management programs to ensure that risk assessment is included as part of the planning of product realisation; reference SOP 7.1, Risk Management. The Risk Management File is updated as changes to the Quality Management System are made. ISO 14971 is used as a guidance document for risk management activities. The output from product realisation planning includes all of the forms, procedures, technical documentation, and other records associated with the development of products and processes.

Procedures Relating to Clause 7.1 Planning of Product Realisation	
SOP 7.5	Control of Outsourced Manufacturing
SOP 7.4	Purchasing and Vendor Management
SOP 4.2	Document Control Procedure
SOP 8.3A	Control of Non Conformances
SOP 7.3A	Design Control
SOP 8.5	CAPA
SOP 7.1	Risk Management

7.2 End User Related Processes

7.2.1 Determination of Requirements

The BDRG ensures that end user requirements are identified including:

- Requirements specified by the end user, including the requirements for ergonomics, environmental conditions, tolerances and other operational related requirements.
- Requirements not stated by the end user but necessary for specified use or known and intended use.
- Statutory and regulatory requirements related to the product.
- Any additional requirements necessary to ensure the end user's satisfaction, such as providing technical information or specific documentation.

7.2.2 Review of Requirements related to the Product

The BDRG personnel ensure that all requirements related to the device development are identified and documented. This is implemented during the design process, which is used to verify and approve the design inputs and outputs.

Records of requirement review and actions arising from the review are maintained. Where product requirements are changed, the BDRG personnel shall ensure that all the pertinent documents are amended and that relevant personnel are informed of the changed requirements.

7.2.3 End User Communication

Management has implemented effective arrangements for communicating with end users in relation to:

- Product information, including details about products, sales and service information.
- Enquiries, contracts, or order handling, including amendments.
- User feedback, including clinical engagement.

Procedures Relating to Clause 7.2 Customer Related Processes	
SOP 7.3A	Design Control
SOP 7.5A	Control of Outsourced Manufacturing

7.3 Design and Development

7.3.1 Design and Development Planning

Design control procedures including design verification and validation procedures are maintained. Product development procedures are intended to balance the freedom to innovate and the discipline required to consistently meet user and regulatory requirements. Design activities prior to the formal documentation of design inputs are at the discretion of the engineer, and records are kept in laboratory notebooks. Subsequent to the formal establishment of the design inputs, design activities are planned, controlled, and regularly reviewed.

7.3.2 Design and Development Inputs

During the planning phase of product development, inputs related to product requirements will be determined. SOP 7.3.2 Defining Design Inputs procedure has been established to outline this activity. Design inputs are collected from many sources, including users, key opinion leaders (KOLs) in the field of use, similar products, and others. These inputs will form the basis for a Design History File (DHF) for that design. These Design History Files will become the main record of all product development performed at later stages of the design process.

Design Inputs will include:

- Functional, performance, and safety requirements as applicable to the intended use.
- Any statutory and regulatory requirements that apply to the product.
- Information relating to existing designs that are similar to the new product.
- Risk assessment information as applicable.

Inputs of the design development process will be reviewed and approved after they have been determined. This review is intended to ensure that the requirements are complete, unambiguous and not in conflict with each other.

7.3.3 Design and Development Outputs

Design outputs are documented and are compared to design inputs to ensure that input requirements are met. Design outputs may include, but are not limited to, design specifications, engineering drawings, laboratory notebooks, SOP's, forms, testing and technical reports. Design outputs are reviewed and approved particularly before clinical evaluation.

These outputs will also include documentation related to the safety and performance characteristics of the product where appropriate that are essential for its safe and proper intended use. All design output records are included in product Design History Files.

7.3.4 Design and Development Review

SOP 7.3A Product Design Control procedure includes the requirements for design review. During the course of design development, reviews of existing information about a new design will be discussed and reviewed with appropriate personnel to ensure that any problems are identified and corrected so that the product can meet all stated requirements. Records of all design reviews are included in Design History Files as design review minutes.

Participants in design reviews shall include representatives of functions involved with the design phase being reviewed, as well as other specialist personnel who may be required to provide technical input such as clinicians.

7.3.5 Design and Development Verification

Design and development output will include all relevant information necessary to verify that the new product meets all stated development input requirements. Through the design and development system established by management, this verification is performed and the results are approved and recorded. All stages of the design and development process are recorded in relevant Design History files, ensuring that a complete history of a product's development is available for review. SOP 7.3.3 Design Verification and Product Validation procedure outlines the requirements for this activity.

7.3.6 Design Validation

In addition to design verification, the design and development system also ensures that product designs are validated during the final stages of the development process. This validation ensures that the final product is able to meet all of the performance and safety requirements for the intended use/application of the product. Validation also includes an evaluation of performance of the final product. Records of this validation are maintained as part of a Design History File. Validation is completed before release of the final product from Product Development. SOP 7.3.3 Design Verification and Design Validation procedure outlines the requirements for this activity. Product validation may include the performance of clinical evaluations and/or evaluation of the performance of a medical device, as required by national or regional regulations.

7.3.7 Control of Design and Development Changes

Changes to existing designs are reviewed, verified, and validated before they are approved and implemented, as per SOP 4.2.3 Change Control. This review will ensure that the finished product, as well as components for the product will continue to function as intended. All design changes are documented within individual Design History Files. SOP 4.2.3 Change Control procedure outlines the controls around Design Changes.

Procedures Relating to Clause 7.3 Design and Development	
SOP 7.3A	Product Design Control
SOP 7.3.2	Defining Design Inputs
SOP 7.3.3	Design Verification and Design Validation
SOP 7.3B	Design History File Preparation
SOP 7.3C	Technical File Preparation and Maintenance
SOP 4.2.3	Change Control
SOP 7.1A	Risk Management

7.4 Purchasing

7.4.1 Purchasing Process

As the BDRG is a part of UCC, it uses the procurement policies and procedures of UCC, under the University's ISO 9001 certified quality management system. This complies with national public procurement guidelines and rules.

The BDRG ensures that purchased products conform to specified purchase requirements. UCC evaluates and selects suppliers based on their ability to supply products and services in accordance with requirements. Records of supplier performance and supplier evaluation are retained on file and are reviewed as part of the UCC Management Review process.

In addition to the University polices, the BDRG evaluates all new suppliers with regard to their quality and process capability and where applicable, compliance with ISO13485. SOP 7.4 Purchasing and Vendor Management Procedure has been established and implemented to ensure that purchased material conforms to the specified purchase requirements. This

procedure does not apply to the suppliers of equipment or materials not unique to medical device design such as stationery, printing or office supplies.

The criteria for selection of suppliers are defined in SOP 7.4 Purchasing and Vendor Management Procedure. Suppliers which meet the criteria will be approved and added to the Approved Vendor List (AVL). Products and/or services may be purchased only from suppliers who are listed on the Approved Vendor List. Materials which are purchased before "design freeze" stage do not necessarily need to be from suppliers on the AVL.

Quality performance of suppliers is monitored by delivery time and quality of received goods, and this is reviewed at the management review meeting. Suppliers demonstrating inadequate performance may be asked to implement corrective action. Where there is no improvement in performance, the supplier will be removed from the Approved Vendor List. Records of supplier evaluations and performance are maintained in accordance with SOP 4.2 Document Control Procedure.

7.4.2 Purchasing Information

Purchase orders (PO) are placed via the UCC Agresso online payment system. PO'S are automatically generated once the vendor has been approved and added to the Agresso database and the raised requisition has been approved by the project code approver. The PO should include product information described in the product text section of the requisition entry.

7.4.3 Verification of Purchased Material

Prior to issue, all purchased material within the scope outlined in SOP 7.4 Purchasing Procedure shall be verified to ensure that the material meets specified purchase requirements. If the BDRG wishes to perform verification at the supplier's premises, the verification arrangements and method of verification shall be documented. Records of the verification are maintained as per SOP 4.2 Document Control procedure.

Procedures Relating to Clause 7.4 Purchasing	
SOP 7.4	Purchasing and Vendor Management Procedure
SOP 7.4.1	Supplier Auditing Procedure
SOP 4.2	Document Control Procedure

7.5 Production and Service Provision

7.5.1 Control of Production and Service Provision

7.5.1.1 General Requirements

The BDRG does not place products on the market or distribute commercialised medical devices. However the BDRG has established procedures necessary to plan and carry out production of medical devices for clinical investigation purposes.

Controlled conditions may include, but are not limited to, the following (as applicable):

- The availability of information that describes the characteristics of the product, including relevant documentation required by national or international regulations (such as Device Master Records or Technical Files).

- The availability of SOP's at Point of Use to the personnel that require them, including reference materials and/or measurement standards.
- The requirements for equipment where that equipment could affect the performance or safety of the product or the safety of personnel.
- The availability and use of monitoring and measuring devices, particularly for the testing and/or verification of medical devices that have a measurement function.
- The implementation of monitoring and measurement, including the inspection of incoming materials, in process products, and finished products.
- The implementation of release, delivery, and post-delivery activities.
- Labeling and packaging requirements and any special environmental controls or employee training necessary to ensure product conformity.

Management has established the necessary processes to record traceability information for each batch of BDRG products used in a clinical setting to ensure that safety or performance issues can be appropriately addressed. These records include the amount manufactured, production history, inspection status information, and amount released for distribution. Batch records are verified and approved.

7.5.1.2 Control of production and service provision – specific requirements

7.5.1.2.1 Cleanliness of product and contamination control

The manufacture and sterilisation of BDRG products are outsourced to a qualified subcontractor, see;

- SOP 7.4 Purchasing and Vendor Management Procedure
- SOP 7.5 Control of Outsourced Manufacturing

7.5.1.2.2/7.5.1.2.3 Installation and Servicing Activities

The BDRG does not carry out installation or servicing activities and is not applicable, please see section 1.2.

7.5.1.3 Particular Requirements for Sterile Medical Devices

The BDRG maintains records of the process parameters for the sterilisation process which is used for each sterilisation batch. Sterilisation records are traceable to each production batch of medical devices. Sterilisation activities are outsourced to a suitably qualified subcontractor.

Procedures Relating to Clause 7.5.1 Control of Production and Service Provision	
SOP 7.4	Purchasing and Vendor Management Procedure
SOP 7.5	Control of Outsourced Manufacturing

7.5.2 Validation of processes for production and service provision

7.5.2.1 General Requirements

Any process that cannot be verified by subsequent monitoring or measurement will be validated prior to its acceptance as a standard manufacturing process. This validation includes any processes where deficiencies become apparent only after the product is in use. This validation will demonstrate the ability of the processes to achieve planned results. Records of any validation will be maintained as part of the BDRG Quality Management System.

Process validation activities are carried out by the outsourced manufacturer as approved by the BDRG Principal Investigator.

The outsourced manufacturer process validation procedures shall include;

(a) defined criteria for review and approval of the processes,

(b) approval of equipment and qualification of personnel,

(c) use of specific methods and procedures,

(d) requirements for records, and

(e) re-validation.

Procedures Relating to Clause 7.5.2 Process Validation	
SOP 8.5.1B	Customer Complaints Handling
SOP 4.2	Document Control
SOP 4.2.4	Quality Records

7.5.3 Identification and traceability

7.5.3.1 Identification

The ability to trace a batch of product back to all raw materials used in its manufacture and to trace any lot of raw material to products it became part of is an essential feature of our Quality Management System. A part number and lot number control of all materials is used to manufacture products. This provides complete traceability from receipt of raw materials through final shipment to the end user. For all devices, the part number and lot number will be printed on each individual device. Management is responsible for assigning part numbers.

Where manufacturing of the device is outsourced, subcontractors shall demonstrate their ability to provide product through using a suitable traceability system. Where medical devices are returned, SOP 8.3A Control of Non-Conformances shall be used to ensure that medical devices returned to the organisation are identified and distinguished from conforming product.

7.5.3.2 Traceability

7.5.3.2.1 General

Traceability is maintained on all our products, from raw material to finished goods, with a unique identifier on the product. The BDRG has overall responsibility for the coordination of all traceability management systems, which will be managed directly by the body responsible for handling the components and products; outsourced manufacturer and distribution agents. This is referenced in SOP 7.5A Control of Outsourced Manufacturing procedure.

7.5.3.2.2 Particular Requirements for active Implantable Medical Devices and Implantable Medical Devices

The BDRG does not manufacture or supply implantable or active implantable devices, therefore this clause is not applicable, please see section 1.2.

7.5.3.3 Status Identification

The BDRG ensures that the product status with respect to monitoring or measuring requirements is identified. Where manufacturing is outsourced, the BDRG ensures that this activity is maintained at the supplier premises through design transfer, supplier approval and

auditing activities. Product status shall be identified throughout production and storage of the product in order to ensure that only product which has passed the required inspections and tests (or released under authorised concession) is dispatched or used.

Procedures Relating to Clause 7.5.3 Identification and Traceability	
SOP 8.3A	Control of Non Conformances
SOP 7.5	Control of Outsourced Manufacturing

7.5.4 Customer Property

The BDRG shall exercise all due care with customer property while they are under the group's control or being used by the group. If customer property is lost, damaged or otherwise found to be not suitable for use, the BDRG shall report this to the customer according to SOP 8.3A Control of Non-Conformances and maintain records according to SOP 4.2 Document Control Procedure.

Customer property can include intellectual property or confidential health information.

Procedures Relating to Clause 7.5.4 Customer Property	
SOP 7.5.2	Process Validation and Equipment Qualification Requirements for Suppliers
SOP 4.2	Document Control

7.5.5 Preservation of Product

Procedures have been established to ensure that products and components will be preserved throughout the manufacturing process to ensure product conformity with specifications. These procedures include identification, handling, packaging, storage and protection and will be in effect up to and including the time of delivery to the intended destination. Where applicable, these procedures also include environmental controls to ensure that factors in the environment do not degrade the quality of BDRG products or components.

Management procedures or documented work instructions to ensure that products with limited shelf lives or components with limited shelf lives are monitored to ensure that expired products or components are not used in manufacturing processes. Any special storage conditions shall be controlled and recorded.

Raw materials, sub-assemblies or final product are not stored in the BDRG premises; these are under the control of the contract manufacturer and sterilisation provider, both of whom are certified to ISO 13485 requirements.

Procedures Relating to Clause 7.5.5 Preservation of Product	
SOP 4.2	Document Control Procedure
SOP 8.3A	Control of Non Conformances
SOP 7.5	Control of Outsourced Manufacturing Procedure
SOP 7.4.3	Laboratory Material Management

7.6 Control of Monitoring and Measuring Devices

A documented procedure outlines controls employed by the BDRG to manage measuring devices. Equipment subject to calibration shall be positively identified by means of a label indicating, at a minimum, the date calibrated, the due date for the next calibration and the person who performed the calibration. A Master List of Gauges is maintained, which states whether the equipment is calibrated internally or externally, or for reference purposes only.

Where necessary to ensure valid results, measuring equipment shall;

- Be calibrated or verified (or both), at specified intervals or prior to use, against measurement standards traceable to international or national measurement standards; where no such standards exist, the basis for calibration or verification shall be recorded. This record shall be maintained according to SOP 4.2.4 Quality Records Procedure;
- Be adjusted or re-adjusted as necessary;
- Be identified in order to determine its calibration status;
- Preventative maintenance completed in line with manufacturers recommendations;
- Measurement equipment needs to be operating within the appropriate range as recommended by the manufacturers;
- Be safeguarded from adjustments that would invalidate the measuring result;
- Be protected from damage and deterioration during handling, maintenance and storage.

In addition, the BDRG will assess and record the validity of the previous measuring results when the equipment is found not to conform to requirements. Records of the results of calibration and verification are maintained.

Where computer software is used for monitoring or measurement, the ability of the computer software to satisfy the intended application shall be confirmed.

Procedures Relating to Clause 7.6 Control of Monitoring and Measuring Devices	
SOP 7.5.2	Process Validation and Equipment Qualification Requirements for Suppliers
SOP 7.5	Control of Outsourced Manufacturing Procedure
SOP 6.3	Calibration and Equipment Maintenance

8.0 Measurement, Analysis and Improvement

8.1 General

The BDRG plan and implement the monitoring, measurement, analysis and improvement processes needed to:

- Demonstrate that the device conforms to requirements.
- Ensure conformity of the quality system, and
- Continually improve the effectiveness of the quality system.

The effectiveness of the quality system is monitored by internal audits, the monitoring of quality objectives, the management review process and by monitoring user feedback. Results of these activities are reported to management and are used to identify opportunities for improvement.

Procedures Relating to Clause 8.1 General	
SOP 5.6	Management Responsibility Procedure
SOP 8.4	Quality Review Meeting

8.2 Monitoring and Measurement

8.2.1 Feedback

The BDRG ensure that monitoring of end user satisfaction is carried out on an ongoing basis. This is carried out via:

- Feedback during management meetings;
- User feedback; and
- Corrective and preventive action is carried out to enhance user satisfaction as required.

8.2.2 Internal Audit

SOP 8.2.2 Internal Auditing Procedure has been established and maintained for planning and implementing quality audits to verify whether quality activities and related results comply with planned arrangements, to the requirements of ISO 13485, Medical Device Directive 93/42 EEC and to the BDRG's established quality management system. The audit process is also intended to determine if the quality management system is effectively implemented and maintained. Internal quality audits shall be carried out on a regular and systematic basis and are scheduled on the basis of status and importance of the activity to be audited.

The internal audit process is intended to ensure that the BDRG is compliant with the following standards and regulations;

- ISO 13485 Quality management system requirements for Medical Devices.
- BDRG quality management system requirements.
- Medical Device Directive 93/42/EEC of the European Union as it applies to the Quality Management System.

8.2.3 Audit Schedule

All activities relevant to the quality system are audited once per year to determine the effectiveness of the system. The internal audit plan shall reflect the status (based on results from previous audits) and importance of the processes and areas being audited. Audit frequency must be increased in response to non-conformances and, where appropriate, user complaints. The audit criteria, scope, frequency, methods, responsibilities and requirements for planning and conducting audits, and for reporting and maintaining results, are defined and documented in SOP 8.2.2 Internal Auditing Procedure.

8.2.4 Audit Results

The results of internal audits shall be recorded and presented to management, who is then responsible for addressing any non-conformities which may have arisen without delay.

Corrective actions arising from internal audits shall be verified and the results of this verification shall be reported at the management review meeting.

Internal quality audits shall be carried out by trained personnel assigned by management and auditors must be independent of the function being audited. The internal audit function may also be outsourced to a suitably qualified external auditor.

8.2.5 Monitoring and Measurement of Processes

The robustness of the quality management system is measured and monitored by internal quality audits and during the management review process. Identification of improvements to processes or the continued suitability of processes is assessed during these audits and the identification of possible improvements/corrective actions is determined. Some of the key processes that are monitored are as follows:

- Internal quality audits
- Other internal audits
- User satisfaction
- Product acceptance/ non-conformance
- Management review process

The intended purpose of these key processes is quantified by their output, for example conformance to device specifications.

8.2.4 Monitoring and Measurement of Product

8.2.4.1 General Requirements

The BDRG monitors and measures a range of characteristics of the product to verify that product requirements are met. This will be carried out at appropriate stages of the product realisation process in accordance with planned arrangements and documented procedures.

Evidence of conformity of the product with the acceptance criteria is maintained. Records also indicate the person(s) authorising the release of the product.

8.2.4.2 Particular Requirements for Implantable Medical Devices

The BDRG does not manufacture or supply implantable or active implantable devices, therefore this clause is not applicable, please see section 1.2.

Procedures Relating to Clause 8.2 Monitoring and Measurement	
SOP 7.1A	Risk Management
SOP 8.2.2	Internal Auditing
SOP 8.5.1A	Adverse Event Reporting
SOP 5.6	Management Responsibility
SOP 7.4	Purchasing and Vendor Management
SOP 8.4	Quality Review Meeting

8.3 Control of Non-Conforming Material

The BDRG has established documented procedure for the control of non-conformances; SOP 8.3A Control of Nonconformances. The scope of this procedure does not include nonconforming material or product in a supplier's facility, which shall be controlled under the supplier's Quality System (see SOP 7.5 Control of Outsourced Manufacturing).

Non-conforming product which has left the suppliers facility is dealt with in the following procedure;

- SOP 8.3B Product Field Action Procedure

When nonconforming product is detected after delivery or use has started, appropriate actions to the effects (or potential effects) of the nonconformity will be taken through the BDRG corrective/preventive action system SOP 8.5 CAPA Procedure. These actions will be documented and records will be included as Quality Records. A review of the SOP 7.1 Risk Management File shall take place in light of user complaints due to the detection of nonconforming product.

In the event of rework, the rework activity shall be documented in an instruction which has undergone the same authorisation and approval as the original work instruction. Prior to authorisation and approval of the rework instruction, a determination of any adverse effect of the rework upon product shall be made and documented

Procedures Relating to Clause 8.3 Control of Non-Conforming Product	
SOP 8.3A	Control of Non-Conformances Procedure
SOP 7.5	Control of Outsourced Manufacturing
SOP 8.3B	Product Field Action
SOP 8.5	CAPA
SOP 7.1A	Risk Management

8.4 Analysis of Data

The BDRG has established documented procedures to determine, collect and analyse appropriate data to demonstrate the suitability and effectiveness of the quality management system and to evaluate if improvement of the effectiveness of the quality management system can be made. This review shall include data generated as a result of monitoring and measurement and from other relevant sources such as;

- User feedback;
- Product conformity;
- Internal audit results;
- Non-conformances;
- Process and product characteristics and trends;
- Opportunity for preventive action;
- Supplier data.

Records of data analysis are maintained as quality records.

Procedures Relating to Clause 8.4 Analysis of Data	
SOP 5.6	Management Responsibility Procedure
SOP 8.4	Quality Review Meeting
SOP 7.5	Control of Outsourced Manufacturing

8.5 Improvement, Corrective and Preventive Action

8.5.1 General

The BDRG has a system to identify and implement any changes necessary to maintain the continued suitability and effectiveness of the quality management system through the following;

- The quality policy;
- Quality objectives;
- Internal and external audit results;
- Analysis of data;
- Corrective and preventive actions;
- Management review meetings.

The BDRG has established a documented procedure for the review and reporting of adverse events which meet defined reporting criteria to regulatory authorities; SOP 8.5.1A Adverse Event Reporting. This procedure shall take in the different regulations depending on the territory in which the product is to be distributed.

8.5.2 Corrective Action

Corrective action is recognised as a key element in the continued improvement of the quality management system. Corrective actions are taken to eliminate the causes of an existing non-conformance, or other undesirable situation in order to prevent recurrence. This procedure is outlined in SOP 8.5 Corrective and Preventive Action Procedure.

The principal investigator ensures adequate resources are available to identify and implement corrective and preventive actions.

SOP 8.5 Corrective and Preventive Action Procedure defines the requirements for:

- Reviewing nonconformities, including customer complaints;
- Determining the causes of nonconformities;
- Evaluating the need for action to ensure that nonconformities do not recur;
- Determining and implementing action needed including, as appropriate, updating documentation;
- Records of the results of any investigation and of action taken;
- Reviewing the corrective action taken and its effectiveness.

All User complaints are logged, and an investigation is carried out to determine the root cause of the complaint. The QA/RA Administrator is responsible for ensuring that user complaints are

followed up by checking the status on a monthly basis. An analysis of user complaints is carried out at each Management Review meeting.

8.5.3 Preventive Action

The need for preventive action is determined on the basis of information and data gathered regarding performance of processes, nonconformity rates, user returns and complaints, and quality system audit findings. Appropriate information and data is collected and analysed to detect unfavorable trends that, if not checked, will increase the risk of nonconformities. The steps required to eliminate potential non-conformities shall be determined and documented. When implemented, the actions shall be reviewed for effectiveness and shall form part of the Management Review. Preventive actions taken shall be appropriate to the effects of the potential problems.

SOP 8.5 Corrective and Preventive Action Procedures define requirements for;

- Determining potential nonconformities and their causes;
- Evaluating the need for action to prevent occurrence of nonconformities;
- Determining and implementing action needed;
- Records of results of any investigation and of action taken;
- Reviewing preventive action taken;
- Reviewing preventive action taken and its effectiveness.

Procedures Relating to Clause 8.5 Improvement, Corrective and Preventive Action	
SOP 5.6	Management Responsibility Procedure
SOP 8.5	Corrective and Preventive Action Procedure
SOP 8.5.1A	Adverse Event Reporting
SOP 8.3B	Product Field Action

9. Revision History

CC No.	Superseded text	Updated text	Revision	Date
N/A	N/A This is the first issue of this document.	N/A This is the first issue of this document.	N/A	N/A

10. Attachments

[Not included in this sample]

Appendix 2 – SecuRetract Technical File Part A

(Uncontrolled Sample)

TECHNICAL FILE

Document No.: TF-02 Part A

Project Name: SecuRetract

Revision No.: [UNCONTROLLED SAMPLE]

BIOMEDICAL DESIGN RESEARCH GROUP

SECURETRACT TECHNICAL FILE PART A – Product Summary

Approvals

The signatures below certify that this procedure has been reviewed and accepted, and demonstrates that the signatories are aware of all the requirements contained herein and are committed to ensuring their provision.

	Name	Signature	Position	Date
Reviewed by			[insert position]	
Approved by			[insert position]	

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Note: The Biomedical Design Research Group (BDRG) is a core research group in the School of Engineering at University College Cork. The group's primary purpose is to identify and solve unmet clinical needs through user-centred design in keeping with best industrial practices for the development of medical devices. Under the current remit of the BDRG, medical devices will be design and developed within a QMS compliant with the design control requirements of EN ISO13485. It is not the intention of the BDRG to become the legal manufacturer. Therefore the purpose of this Technical File is to describe the product specific design activities that may be by a future manufacture before proceeding to fulfil the regulatory requirements to place the device on the market.

1.1. Administrative Details

1.1.1 Organisational Information

[To be completed on transfer of this document to legal manufacturer]

1.1.2 Notified Body

[To be completed on transfer of this document to legal manufacturer]

1.1.3 Certification

[To be completed on transfer of this document to legal manufacturer]

1.1.4 Declaration of Conformity

Revision	[Completed on transfer]
Legal Manufacturer's Name	[Completed on transfer]
Legal Manufacturer's Name	[Completed on transfer]
Product Name and Description	SecuRetract is a minimally invasive laparoscopic mesenteric bowel retractor which is introduced into the peritoneal cavity via a surgical cannula and has duration of continuous use of less than 60 minutes. The contact area which is exclusive to the distal portion of the device comprises a number of inflatable balloons which provide a soft interface with the internal organs. The intended use of the retractor is to surround the bowels by forming a semi-circular curved profile, and retracting said bowel from the operating field. On conclusion of the procedure, the retractor is disposed of. The device is actuated by a manual mechanical means.
Product Code	GCJ
Classification	IIa (CE), II (FDA)
Device risk class	Medium Risk

I the undersigned, hereby declare that the medical device(s) described above and bearing the CE marking, conform to the applicable provisions of EC Medical Device Directive 93/42/EEC, complies with the

applicable principles of safety and performance, has met the applicable conformity assessment elements and are therefore eligible to bear the CE marking as defined therein.

Signature: _____

Full Name Printed: _____

Position: _____

Date: _____

Place: _____

1.2. Product Description

1.2.1. Device Identification

1.2.1.1. SecuRetract Classification

SecuRetract is a minimally invasive laparoscopic retractor which is introduced into the peritoneal cavity via a surgical cannula and has duration of continuous contact of less than 60 minutes (i.e. *Transient Use*). The contact area which is exclusive to the distal portion of the device comprises a number of inflatable balloons which provide a soft interface with the internal organs. On conclusion of the procedure, the retractor is disposed of. The device is actuated by a manual mechanical means. SecuRetract may therefore be deemed as a *Surgically Invasive Device* as the distal end of the retractor both enters and exits through an artificially created opening (i.e. a surgical cannula).

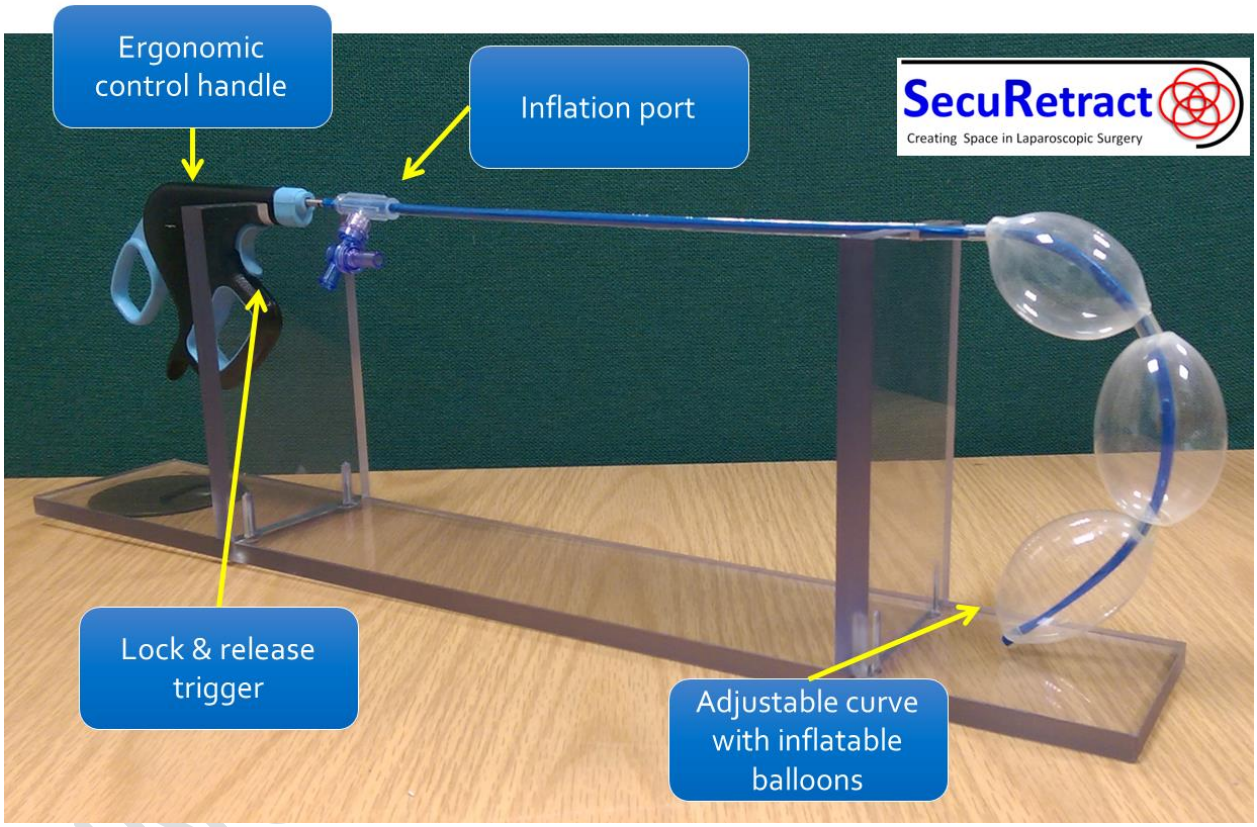


Figure 1. SecuRetract laparoscopic retractor pictured in the inflated and curved position

SecuRetract is classified as a Class 2a device via classification rules defined within the Annex IX of European Directive 93/42/EEC as amended, and schedule 9 of related Irish regulation (S.I. No. 252/1994), and in particular to rule seven pertaining to surgically invasive devices for short term use. Conformity can be achieved through a notified body subsequent to adhering to Annex II of the Medical Device Directive 93/42/EEC.

For FDA Classification guidelines, a device which falls with the controls of product Code GCJ, associated with endoscope and accessories, may be deemed as a class 2 device. A number of predicate Class 2 devices such as the A-Lap™ retractor (EZsurgical, 510(k) application K082291) and the ExtraHand™ balloon

retractor (Medtronic, 510(k) K962005) have been identified. Premarket notification 510(k) is the most direct route for regulatory approval in the U.S. and substantial equivalence may be shown to a predict devices such as the A-Lap retractor.

Table 1 provides a list of deployable retractors which have gained regulatory approval from the FDA via a 510(k) approval process. The table also lists the classification for each retractor which in each case is a Class II device.

Table 1 Examples of existing device approvals and classification type

Device	Company	Retractor Type	Class	510(k) Number
A-Lap™ Retractor	EZsurgical	Deployable	II	K082291
Laparoscopic Balloon Retractor	Origin Medsystems INC	Balloon	II	K926480
ExtraHand™ Balloon Retractor	Origin Medsystems INC	Balloon Retractor	II	K962005
Laparoscopic Retractor	Surgical Innovations	Snake Retractor	II	K112659
Laparoscopic Retractor	Cardinal Health INC	Snake Retractor	II	K092684
Karl Stortz Pivot Arm Lap Sleeve, Endo-Retractor	Karl Stortz	Retractor	II	K946330
Laparoscopic Surgical Retractor	Advanced Surgical	Retractor	II	K933032
Virtue Male Sling System with Alexis Wound Retractor	Coloplast Corp.	Sling	II	K111881
Mini Lap Retractors	Mini Lap Technologies	Graspers	II	K093449
Aesculap Sovereign mini system	Aesculap	Graspers	II	K123102

1.2.1.1. Conformity assessment procedure

Article 11(2) of Council Directive 93/42/EEC concerning Class IIa medical devices describes the conformity assessment process. In the case of devices falling within Class IIa, other than devices which are custom-made or intended for clinical investigations, the route to conformity may follow CE Declaration of conformity (Annex II MDD 93/42/EEC) (see Figure 2).

1.2.1.2. Products Covered

The product covered under this Technical File is SecuRetract, a novel, atraumatic retractor used in laparoscopic surgery.

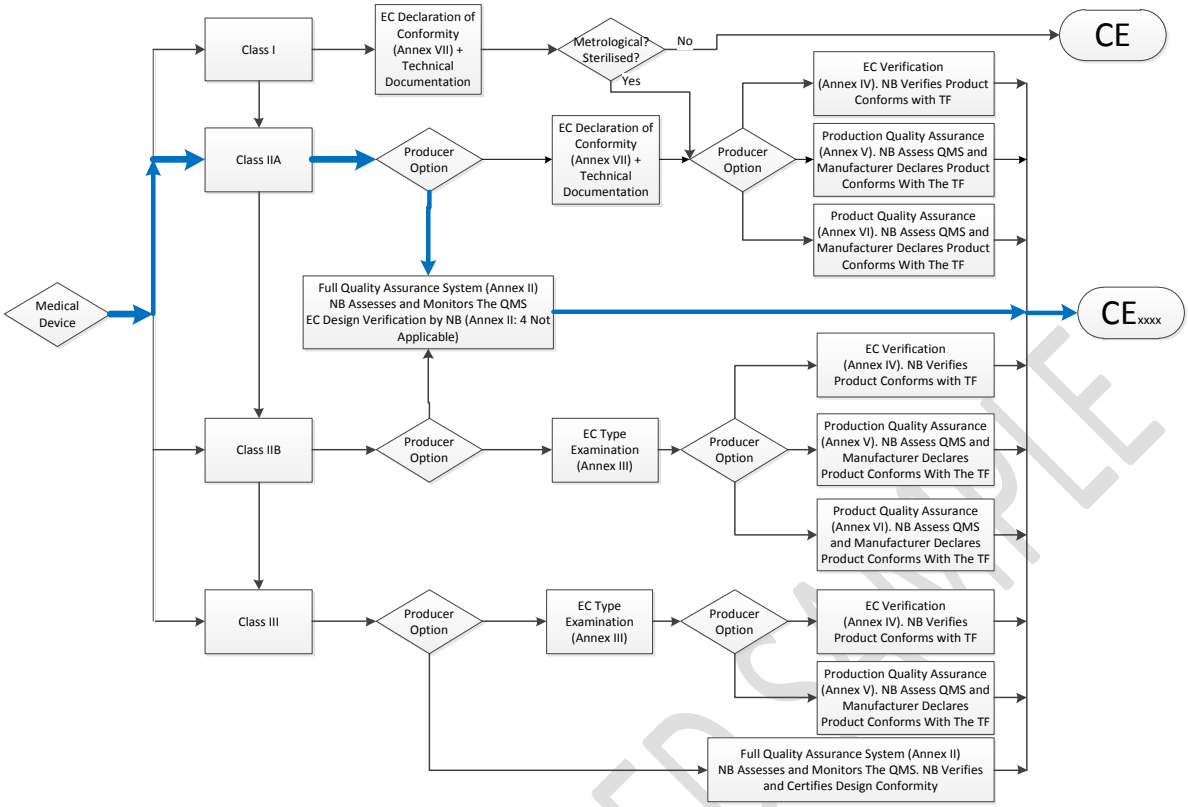


Figure 2. Flow chart for conformity assessment procedures for medical devices as provided for in MDD 93/42/EEC

1.2.2. Device Description

1.2.2.1. Intended use

SecuRetract is a minimally invasive, disposable, deployable, mesenteric bowel retractor for the use in laparoscopic surgery. One of the most common challenges encountered during laparoscopy is that of the distended loops of bowel or overlaying organs spilling into the operating field and thus obstructing the surgeon's view. SecuRetract can be inserted into the peritoneal cavity through a surgical cannula in its deflated state. Once the region of interest has been identified, the impeding organs are retracted by manipulating the device until it hooks around these organs. The device is then inflated, increasing the contact area and finally withdrawn from the operating field, retracting the organs in the process. During the installation of SecuRetract, the patient may be placed in the Trendelenburg position (steep head down) to assist in placement. After the retractor is inserted, the distal tip, comprising a leaf spring sheathed within flexible extruded tubing, may be curved creating a hook shape by actuating the control handle. The radius of curvature may be modified as required and the retractor is placed between the bowel and its attached mesentery. The distal end of SecuRetract is then inflated increasing the contact area between the retractor and the bowels as well as creating a soft interface due to the cushioned effect of the modular balloons. As a result of the increased contact area and the curved profile of the retractor, a more effective withdrawal of the distended loops of the bowels can be obtained. Once the device has been positioned, the patient may return to the supine position where he or she can remain for the remainder of the procedure. The device can be deflated and removed back through the surgical cannula without incurring or causing damage. The device can subsequently be reinserted as required and is disposed of once the procedure is complete.

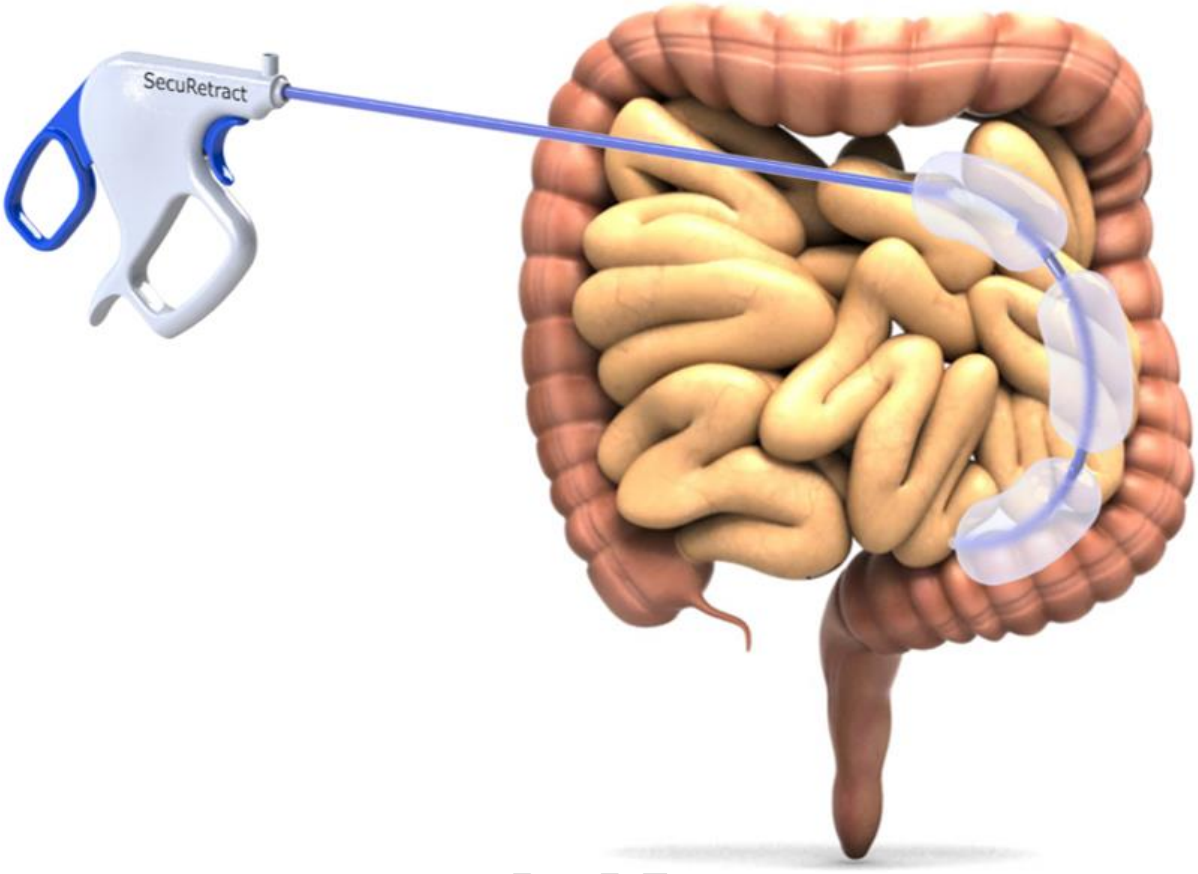


Figure 3. SecuRetract atraumatic retractor illustrating key design features with a computer render of SecuRetract in use

1.2.2.2. Description of device

SecuRetract answers this important clinical need identified by a number of leading colorectal surgeons. SecuRetract is a **minimally invasive, disposable, retractor** for use in laparoscopic surgery with a number of advantages over competing technologies (see Figure 4). This novel retractor has the potential to **ease surgical procedures** as well as **improving patient outcomes** by alleviating a number of common complications currently experienced by the gold standard approach in laparoscopic retraction. SecuRetract facilitates **quick** and **easy insertion** through a small 5 mm instrument port (trocar) though its sleek minimal cross-sectional profile. SecuRetract can be **easily manipulated** to hook around the obstructive organ via an intuitive **ergonomic design** before being inflated to provide a **soft interface** reducing the risk of injury to the soft internal organs. Finally SecuRetract effectively withdraws the obstruction from the operating space providing an essential clear operating space to perform the procedure.

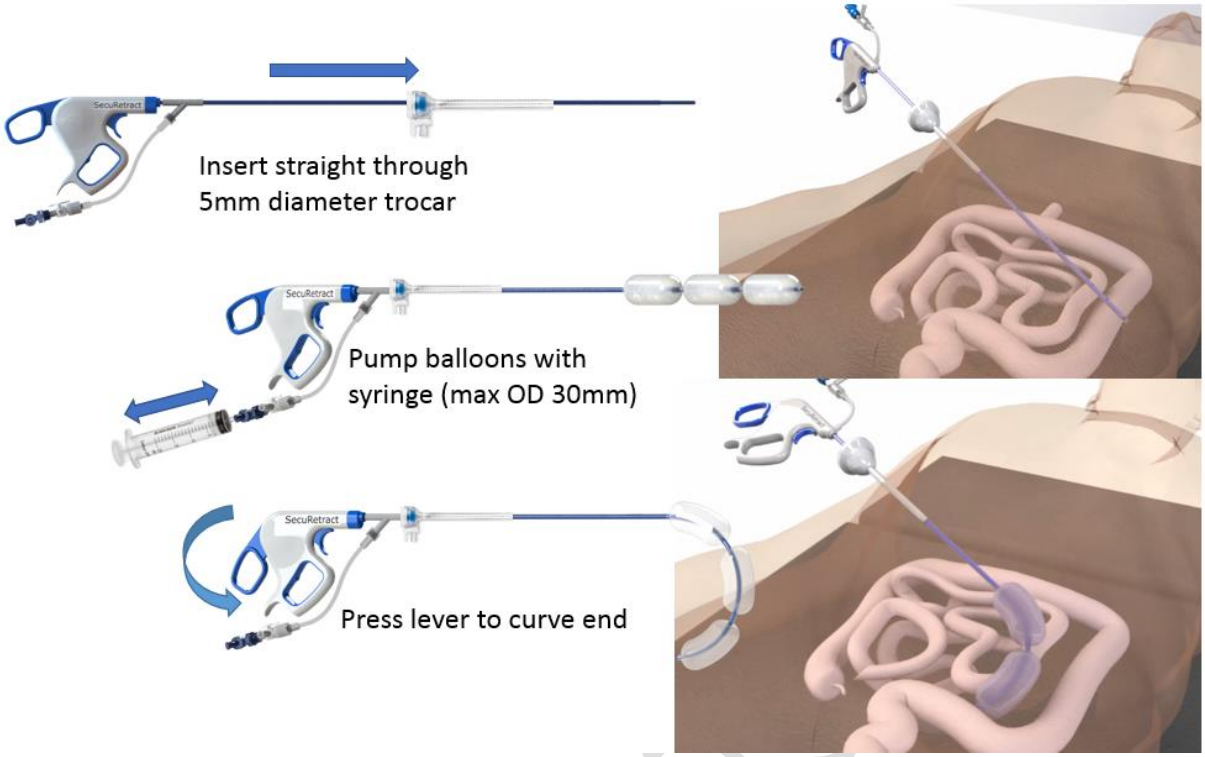


Figure 4. SecuRetract assembly with control handle, shaft and balloons with steps for deployment.

The **hook-shaped inflatable** design is **unique** within the laparoscopic retraction market and provides a **soft interface** for tissue manipulation. Competing devices are generally designed for liver or large organ retraction and lack the capability to effectively retract the messy loops of the small bowel. In addition, SecuRetract is **easily deployed** through a small 5 mm trocar reducing trauma, unlike the 12 mm ports necessary for most competing devices. Finally, the device represents an atraumatic inflatable interface with a high degree of controllability which removes risk of tissue injury during use.

1.2.2.3. Intended user profiles for product

SecuRetract may be used by any member of the surgical team during elective or emergency laparoscopic surgery. The primary clinical indication for this device is bowel retraction during laparoscopic colectomy as a treatment to colorectal cancer. However SecuRetract may also be used to manipulate and retract intrusive internal organs during colon resection for intestinal blockage, ulcerative colitis, intestinal trauma, colon polyps, diverticulitis and ischemic bowel disease. SecuRetract may also be used during alternative clinical applications including hysterectomy, cholecystectomy, prostatectomy, appendectomy and nephrectomy if necessary where the bowel obstructs the surgical field of view.

The initial placement of the retractor is typically performed by the lead surgeon who may then nominate a member of the surgical team to operate the retractor for the majority of its time in use. SecuRetract may also be clamped to the surgical bed thus providing a stand-alone solution. SecuRetract may be removed and redeployed multiple times per procedure and disposed of after the procedure is complete.

1.2.2.4. Summary and explanation of tests, performance evaluation and stability studies

A summary of the design verification and validation is detailed in SecuRetract TF-02 Part B. This summary includes a description of the bench-top testing from both clinical and non-clinical studies and their results,

sterilisation information, biocompatibility study, validation studies and packaging integrity and transportation testing.

1.3. Labels, Packaging and Instructions for Use

1.3.1. Packaging configuration / kit size

The SecuRetract will be placed in a sterilisable pouche with Tyvek back along with a syringe to facilitate inflation of the balloons during administration, and an instructions of use leaflet. Clean room manufactured sterile pouches will be used to protect SecuRetract. The Tyvek barrier allows for EtO sterilisation. One pouche will be placed per box and three box will be placed into an outer carton. The overall box measures 700(l) x 190(w) x 25(h) mm. Depending on market, SecuRetract may also be packaged in separate vacuum formed trays sealed with an air tight lid. The tray will accommodate the SecuRetract in the straight and deflated position. A number of sealed trays may be included per box. The number of trays per box may vary, for example a single box may comprise 3 or 5 units dependent on end user requirements.

[Insert specific detail of sterilisation and packaging suppliers and processes]

1.3.2. Lifetime/shelf life of product and environmental limitations

A critical material for the lifetime of SecuRetract is the elastomeric polyurethane that is used to construct the balloons on the distal end of the retractor. The properties of most rubber and elastomeric materials change as a result of aging. The amount of property change varies with time, environmental conditions and mechanical stress. The environmental conditions include the ambient temperature, the amount of light and the oxygen or ozone to which the materials are exposed during their time in storage. The recommended storage conditions for rubber and elastomeric products according to the Hydril Engineering Bulletin – EB94-001 may be seen in Table 2.

Table 2 Storage parameters for rubber and elastomeric products

Storage Parameter	Recommended Storage	Minimum Acceptable	Unacceptable Storage
Temperature	Less than 27°C	Less than 49°C	Greater than 49°C
Light	Complete darkness	Indirect light	Direct light
Stress	Separate packages	Sacks of loose parts	Pinched, stretched, creased
Environment	Clean dry air	Humid air	Oil, grease and/or water
Oxygen and Ozone	Sealed Package	Open air	Near electric motors

According to the Hydril Engineering Bulletin – EB94-001 polyurethanes have a maximum life under recommended storage conditions of **6 years**. [Insert further detail of shelf life verification]

1.3.3. Labelling

[Insert specific detail and example of labelling]

Note: Labelling serves to communicate safety and performance related information to users of medical devices and/or patients as well as to identify individual devices. Such information may appear on the device itself, on packaging (or as a packaging insert), or as information for use. Annex 1(13.3) of MDD

93/42 EEC outlines the requirements for manufactures to provide sufficient information to use their device safely and properly, taking account of the training and knowledge of the potential users, and to identify the manufacturer.

The label requirements which are applicable to SecuRetract from Annex 1 (13.3) of the MDD 93/42 are {a, b, c, d, e, f, h, I, k}. The label will include the following:
(a) The **name** and **address** of the **manufacturer;**
(b) **Details** necessary **to identify** the **device** and the contents of the packaging especially for the end users;
(c) The word **'STERILE'**;
(d) The **batch code**, preceded by the word 'LOT', **or** the **serial number**;
(e) The **date** by which **the device should be used** expressed as the year and month;
(f) An **indication** that the **device** is for **single use**.
(h) The device is **intended** for **clinical investigations**, the words 'exclusively for clinical investigations';
(i) **Storage** and/or **handling conditions**;
(k) Warnings and/or **precautions to take**;

1.3.4. Instructions for use (IFU)

[Insert specific detail and example of IFU]

Note: Annex 1(13.6) of MDD 93/42 EEC outlines the requirements for manufactures relating to the instructions for use. For Class IIa devices, like SecuRetract, no instructions for use are needed if they can be used without any such instructions (Annex 13.1 MDD 93/42). However, the manufacturer may decide that instructions for instructions are required and will be provided to the end users. The instructions for use will include the following information:

(a) **Details** referred to in Section 1.3.3 of MDD 93/42 for **Labelling**, with the exception of (d) and (e);
(b) The **design**, **manufacturing** and **packaging performances** intended by the manufacturer and any undesirable side effects;
(c) SecuRetract must be **connected** to **other medical devices** (inflation apparatus such as a syringe) in order to inflate the balloons on the distal end;
(d) Information needed to **verify** that the **device** is **properly installed** and **inflated**;
(g) Instructions in the **event of damage to the sterile packaging**;
(h) An indication that the device is for **single use** and **information** on known **characteristics** and **technical factors** known to the manufacturer that could pose a risk if the device were to be re-used;
The instructions for use must also include details allowing the medical staff to brief the patient on any contra-indications and any precautions to be taken. These details should cover in particular:
(k) **Precautions** to be taken in the **event** of **changes in the performance** of the device;
(q) **Date** of **issue** or the **latest revision** of the **instructions for use**.
** The numbering of each requirement corresponds with the requirements listed in section 13.6 of Annex 1 MDD 93/42 EEC.*

1.4. Relevant Regulations

Regulation	Title & Description

MDD 93/42 EEC	European Council Directive Concerning Medical Devices
[insert regulation]	[insert associated title as required]

1.5. Standards/Common Technical Specifications Applied

Standards/ Tech' Spec'	Title & Description
I.S. EN ISO 13485:2012	Medical devices - quality management systems - requirements for regulatory purposes.
I.S. EN ISO 15223-1:2012	Medical devices - symbols to be used with medical device labels, labelling and information to be supplied - part 1.
ISO 15223-2:2010	Medical devices - symbols to be used with medical device labels, labelling and information to be supplied - part 2.
EN 1041:2008	Information supplied by the manufacturer of medical devices.
ISO 11607-1:2006	Packaging for terminally sterilized medical devices - Part 1: Requirements for materials, sterile barrier systems and packaging systems.
ISO 11607-2:2006	Packaging for terminally sterilized medical devices - Part 2: Validation for material, sterile barrier and packaging systems.
[Other as applicable]	[insert associated title as required]

1.6. Internal References

Reference	Title & Description
TF-02 Part B	Securetract Technical File Part B – Proprietary Documentation
BDRG-DHF-02	Securetract Design History File
BDRG-QM	Quality Manual
SOP 7.3 C	Technical File Preparation And Maintenance SOP
[Other as applicable]	[insert associated title as required]

1.7. Revision History

Section	Superseded text	Updated text	Revision	Date
N/A	This is the first instance of this document. There are no revisions	This is the first instance of this document. There are no revisions	[X]	[DD/MM/YYYY]

Appendix 3 – Design File Check List

(Uncontrolled Sample)

Appendix 3 – Design File Check List (Uncontrolled Sample)

Design File Check List **Biomedical Design**
Revision No.: [XX] **Research Group**
ISO 13485 Clause: 7.3
Date: [DD/MM/YYYY]

Design File Reference: _____

A Design File shall be created with the applicable sections. Each applicable section shall be signed off as it is completed.

Design Planning		**Applicable Y/N**	**Responsibility**
1	Project Design and Development Plan (DDP)		

Design Inputs		**Applicable Y/N**	**Responsibility**
1	Marketing Requirement Specification (MRS)		
2	Essential Requirements from 93/42/EEC		
3	Design Information including previous drawings		
4	Intended Use & Device Description		
5	Design FMEA		
6	Device Classification		

Design Outputs		**Applicable Y/N**	**Responsibility**
1	Material Specifications		
2	Final Drawings		
3	Manufacturing Flow Chart and Process FMEA		
4	Components listings (i.e. Bill of Materials (BOM))		
5	Control of vendors for component parts		
6	Work Instructions		
7	Tooling & Equipment		
8	Instructions for Use (IFU)		

Appendix 3 – Design File Check List (Uncontrolled Sample)

Design File Check List **Biomedical Design**
Revision No.: [XX] **Research Group**
ISO 13485 Clause: 7.3
Date: [DD/MM/YYYY]

Design Verification		**Applicable Y/N**	**Responsibility**
1	Development Records		
2	Functional Testing Protocols and Reports		
3	Sterilisation Testing Protocols and Reports		
4	Age & transport testing Protocols and Reports		
5	Bio-compatibility Protocols and Reports		

Design Validation		**Applicable Y/N**	**Responsibility**
1	Animal Trial Information		
2	Clinical Trials Information		
3	Perform Final DFMEA i.e. Residual Risk		

Design Transfer		**Applicable Y/N**	**Responsibility**
1	Manufacturing Work Instructions Present		
2	Training Completed		
3	Device Master Record Present (DMR)		
4	Process Validation Protocols and Reports		
5	Specification present		
6	Process FMEA Completed		
7	Equipment & Tooling Qualifications Complete		
8	CDL's Updated		

As part of the final design review meeting the Quality Assurance Administrator will review this list and the compiled DHF to ensure it has been adequately completed.

Approved By: _____ Date: _____

Appendix 4 – ProDural DFMEA

(Uncontrolled Sample)

APPENDIX 4 - PRODURAL DFMEA (UNCONTROLLED COPY)

Risk Number	ISO 14971 annex ref. if app.	Source; Component, Function or Standard *STEP 1*	Identification of Known or Foreseeable Risks *STEP 2* Potential Hazard	Clinical Effect	Estimation of Risks *STEP 3* Failure source	S	O	Risk Level	Risk Evaluation *STEP 4* Reduction?	Risk Control *STEP 5* Risk Reduction Method	Implementation of Risk Control *STEP 6* Actions for Risk Control	Action taken	Residual Risk *STEP 7* S	O	Risk Level	Other Hazards *STEP 9*
1	C2.1	What is the intended use and how is the medical device to be used?	Injury to the spine and or injection into the subarachnoid space. This hazard exists with current epidural administration techniques. ProDural does not present any increase risk over conventional LOR syringes.	Sever headaches, pneumocephalus, spinal cord and nerve root compression, subcutaneous emphysema, venous air embolism, and neurological injury	Excessive advancement of the epidural needle beyond the epidural space resulting in Dura puncture	4	4	3	Yes	The design of ProDural will reduce the current risk of accidental Dural puncture (ADP) due to the immediate collapse of a visual indicator integrated to the body of the device. End users will receive training and instructions prior to use.	ProDural does not present any deviancy to current practices. The design of ProDural will reduce the incidence rates of ADP. Extensive training and instructions will be issued to end users prior to use.	Improved design and operation over existing LOR syringes whilst maintaining current LOR technique. Instructions attached to each unit.	4	3	2	n/a
2	C2.2	Is the medical device intended to be implanted?	The medical device is not implanted.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
3	C2.3	Is the medical device intended to be in contact with the patient or other persons?	ProDural may be described as an external communicating device as described in section 5.2.2 of ISO10993. The nature of contact is limited to the transfer of fluid from the syringe barrel to the posterior tissue. Possible leaching of material from syringe into the epidural space by way of fluid transfer. This is an existing hazard with conventional LOR syringes. ProDural does not present any increase risk over conventional LOR syringes.	May cause infection if not sterile. Spinal abscess may occur if bacteria enter the epidural space, left untreated may cause paralysis and incontinence.	Device/equipment not sterile prior to use.	3	2	1	Yes	Employ proper sterile techniques using gloves and anti-septic skin preparation. Ensure the device has been effectively sterilised and packaging remains intact prior to administration	Maintain best current practices. Current effective sterile techniques will not be altered	Maintain current best practices in sterility	3	1	1	n/a
4	C2.4	What materials or components are utilized in the medical device or are used with, or are in contact with, the medical device?	Potential biological risk. Potential contamination risk. Potential infection risk. These risks exist presently with conventional methods for epidural administration. ProDural does not present any increase risk over conventional LOR syringes.	Allergic reaction to non biocompatible material. Risk of infection if barrel fluid is non-sterile. Risk of infection/disease transfer if needle is reused.	Chosen construction materials are not biocompatible. Barrel fluid (e.g. saline) is corrupted. If the epidural needle which is attached to the syringe is reused from a previous patient.	4	2	2	Yes	Carry out biological evaluation during design stage to ensure that all materials are compatible. Ensure that all saline used is still in date and the integrity of the container has not been compromised. Never reuse the device. Dispose of all equipment immediately after application.	Biological evaluation. As with current practice, only intact and in-date saline may be used in the application of determining the epidural space and all components are to be discarded after use.	Biological evaluation during design stage. No deviation from current application practices.	4	1	1	n/a
5	C2.5	Is energy delivered to or extracted from the patient?	No energy is delivered to or extracted from the patient.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
6	C2.6	Are substances delivered to or extracted from the patient?	The barrel of the syringe is partially or complete filled with a injection medium (air or saline). This may contain contaminates which may be subsequently injected into the epidural/subarachnoid space. The site may be subsequently aspirated to ensure that CSF is not extracted ensuring correct needle placement. This hazard currently exists with present practices.	May cause infection if not sterile. Spinal abscess may occur if bacteria enter the epidural space, left untreated may cause paralysis and incontinence.	Substance compromised and is no longer sterile. Saline has surpassed its use by date and sterility may no longer be preserved.	3	2	1	Yes	Ensure the device has been effectively sterilised and packaging remains intact prior to administration. All saline used is still within its intended use by date and container is still intact.	Maintain best current practices. Current sterile techniques will not be altered.	Maintain current best practices in sterility	3	2	1	n/a
7	C2.7	Are biological materials processed by the medical device for subsequent re-use, transfusion or transplantation?	No biological materials are processed by this device.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
8	C2.8	Is the medical device supplied sterile or intended to be sterilized by the user, or are other microbiological controls applicable?	The device will be delivered sterile in a sealed packaging. A possible hazard is that the packaging has been compromised during transportation and the device may no longer be sterile.	Possible infection.	Packaging has been compromised during transportation.	3	2	1	yes	Ensure that the device has been securely packaged and sealed prior to transportation. Employ a reputable logistics company.	Establish a quality control system to ensure all the relevant checks are carried out prior to product shipping. Post market surveillance.	Established QMS	2	1	0	n/a
9	C2.9	Is the medical device intended to be routinely cleaned and disinfected by the user?	The device is a disposable device and should be discarded after use.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
10	C2.10	Is the medical device intended to modify the patient environment?	There is no modification to the patient environment. The current epidural administration technique will be employed with the addition of a visual indicator to signal correct epidural space localisation.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
11	C2.11	Are measurements taken?	There are no measurements taken.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
12	C2.12	Is the medical device interpretative?	The medical device is used to identify the epidural space. The device comprises an inflatable diaphragm which immediately collapses when the epidural space is reached. However a premature collapse may be incorrectly interpreted as successful identification of the epidural space.	False positive reading which will fail to deliver pain relief when subsequent drop is administered.	Leakage between layers of fatty tissue during application.	2	4	2	Yes	Correct material selection and age testing carried out prior to final product manufacture. Continual quality controls during manufacture. End user training prior to use to reduce incidence of false positive.	Continual product manufacturing quality controls. End user training programmes. Post market surveillance.	Established QMS	2	2	1	n/a
13	C2.13	Is the medical device intended for use in conjunction with other medical devices, medicines or other medical technologies	ProDural will be used in conjunction with a number of existing components used in epidural administration such as an epidural needle and a catheter. ProDural represents no increase in risk or additional hazard compared to conventional LOR epidural syringes when used with accompanying components.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
14	C2.14	Are there unwanted outputs of energy or substances?	The preferred method for sterilisation is using Ethylene Oxide (EtO). This is commonly used to sterilise plastic syringes such as existing LOR syringes. EtO is a primary irritant and is now classified by the IARC as a known human carcinogen. Exposure to EtO is regulated by the EPA and OSHA.	Irritant and known carcinogen. Exposure is very limited.	Incorrect sterilisation technique not in line with international standards such as ISO 11135	4	2	2	Yes	Document the sterilisation requirements in line with best international practice and ensure a quality control regime is employed during the sterilisation process.	Continual product manufacturing quality controls. Post market surveillance.	Established QMS	4	1	1	n/a
15	C2.15	Is the medical device susceptible to environmental influences?	Extreme high temperatures (>200^{o}C) or extreme cold temperatures (-40^{o}C) may alter the mechanical properties of the device. However at such extremes, the containers holding the device would be destroyed and the device could not be used.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
16	C2.16	Does the medical device influence the environment?	The device does not affect power and cooling, it does not emit toxic materials and it does not generate electromagnetic fields.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
17	C2.17	Are there essential consumables or accessories associated with the medical device?	The device may be sold as part of an epidural kit which would include an epidural needle and catheter as well as other consumables. However there is an exception for the UK market whereby a special connection is required to connect to the epidural needle as described in patient safety alert NPSA/2011/PSA001.	Epidural medicine administered by the intravenous route. Intravenous medicine administered by the epidural route. Intravenous medicine administered by the regional anaesthetic route. Regional medicine administered by the intravenous route.	Mis-connection and wrong route errors. The wide use of the Luer connector design enables wrong route patient safety incidents to occur.	4	2	2	Yes	Develop a safe connector designed for spinal and epidural use only in line with interventional best practice.	Design specification to prevent mis-connection and/or wrong route errors.	Design specification during the design phase.	4	1	1	n/a
18	C2.18	Is maintenance or calibration necessary?	No maintenance or calibration is necessary. The device is delivered fit for use and disposed of directly after application.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a

APPENDIX 4 - PRODURAL DFMEA (UNCONTROLLED COPY)

Risk Number	ISO 14971 annex ref. if app.	Source; Component, Function or Standard	Potential Hazard	Clinical Effect	Failure Source	S	O	Risk Level		Risk Reduction Method	Actions for Risk Control	Action taken	S	O	Risk Level	Other Hazards
19	C2.19	Does the medical device contain software?	The device does not contain software.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
20	C2.20	Does the medical device have a restricted shelf-life?	Natural rubber: 3-5 years. Silicone: 20 years. Data sourced from Table 1 of MIL-HDBK-695 which lists the age resistance generally associated with rubber products.	Mechanical failure	Material deterioration	2	2	1	Yes	Suitable storage conditions controlling temperature and humidity. Product controls. Effective age testing. Product storage and distribution controls.	Carry out age testing. Establish product storage and distribution controls. Indicate shelf life on product labelling	Age testing, establish QMS and post market surveillance, appropriate labelling.	2	1	0	n/a
21	C2.21	Are there any delayed or long-term use effects?	Permanent deformation may occur in the elastomeric diaphragm if excessive pressures are exerted without rupturing the diaphragm.	The diaphragm would not return to a perfectly smooth status once the epidural space has been reached. The inflated diaphragm would still collapse indicating the space has been reached.	Excessive force exerted on the plunger without further advancement of the device.	2	2	1	Yes	Diaphragm material selection to reduce the occurrence of permanent deformation by ensuring the material remains elastic for higher pressures.	Material selection reduction though bench top testing until the most effective material is identified.	Appropriate material selection.	2	2	1	n/a
22	C2.22	To what mechanical forces will the medical device be subjected?	From literature review the estimated pressure experienced in the syringe barrel due to plunger advancement is 37.5 ± 20.0 kPa. However from end user surveys it was concluded that far lower pressures are experienced in practice (approx. 14-20 kPa)	Incorrect localisation of the epidural space/ mechanical failure.	Excessive pressure is exerted leading to diaphragm rupture.	3	3	2	Yes	Diaphragm material selection to reduce risk of rupture at high pressures.	Material selection reduction though bench top testing identifying the most effective material is identified.	Appropriate material selection.	2	2	1	n/a
23	C2.23	What determines the lifetime of the medical device?	Change in the physical properties of the material over time. Change may occur due to temperature, humidity, light, radiation, ozone/oxygen and loading. Physical properties may also be altered during the sterilisation process.	Mechanical failure	Material deterioration	2	2	1	Yes	Suitable storage conditions controlling temperature, humidity, exposure radiation. In addition the device will be stored in a sealed packaged container which will reduce exposure to oxygen and light. Correct sterilisation method to reduce impact on mechanical properties. EtO has little if any effect on the physical characteristics of silicone and rubber.	Carry out age testing at design stage. Establish product storage and distribution controls. Indicate shelf life on product labelling	Age testing, establish QMS and post market surveillance, appropriate labelling.	2	2	1	n/a
24	C2.24	Is the medical device intended for single use?	The device is a disposable device and should be discarded after use. A potential hazard is the device is reused.	Cross contamination	Reuse of device	4	3	2	Yes	The device includes a clip which has to be removed prior to each use indication if the device has been used before. This will be included during design stage.	Design specification to include an indicator to signal that it is the first time the device has been used.	First time use indicator designed during the design and development stage.	4	1	1	n/a
25	C2.25	Is safe decommissioning or disposal of the medical device necessary?	There is no special requirement when disposing of this device. The same disposable procedure currently used should be employed. The device is discarded with the biohazard waste in line with current practice.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
26	C2.26	Does installation or use of the medical device require special training or special skills?	No. The device innovation of visual indication is augmentry & not replacing current LOR techniques. The device is used in exactly the same manner as current LOR syringes & no special training beyond the current best practice is required.	Incorrect use of the device leading to complications such as accidental dura puncture and or false localisation of the epidural space.	Over reliance on the visual indicator with neglect to correct LOR technique. Uncontrolled advancement of the needle	4	2	2	Yes	Suitable training to be carried out prior to use. Instructions to be included with the device.	Create training video and documentation	Create training video and documentation	4	1	1	n/a
27	C2.27	How will information for safe use be provided?	The device is used in a similar manner to current LOR syringes with the addition of a visual indicator. Minimum if any training is required. Hazard of incorrect use.	Incorrect localisation of the epidural space.	Incorrect use of the device	3	2	1	No	n/a	n/a	n/a	3	2	1	n/a
28	C2.28	Will new manufacturing processes need to be established or introduced?	The device will be manufacture using conventional injection moulding methods and sourcing appropriate material for the diaphragm.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
29	C2.29	Is successful application of the medical device critically dependent on human factors such as the user interface	Successful application of the medical device is dependant on the tactile feeling and visual indication once a pressure drop is detected on entering the epidural space. Mechanical stiffness may reduce the effectiveness of determining a pressure drop thus diminishing the performance of the device.	Incorrect localisation of the epidural space which may lead to neurological injury and or failure to deliver pain relief.	Mechanical stiffness when advancing the plunger. Elongation stiffness in inflating the diaphragm. Difficulty holding the device. Difficulty seeing the diaphragm collapse	4	2	2	Yes	The syringe body is constructed in line with conventional LOR syringes and a low friction plunger seal will be employed to ensure fluid plunger transmission. The diaphragm will comprise of a bright colour which enhances visibility.	Ethnographic evaluation to be carried out on the final design to ensure an ergonomic solution. Effective material investigation.	Design evaluation. Material selection.	4	1	1	n/a
30	C2.29.1	Can the user interface design features contribute to use error?	A poor ergonomic design may reduce the effectiveness of the design. However the syringe body is designed in line with existing LOR syringes thus should not present a deficit.	Incorrect localisation of the epidural space which may lead to neurological injury and or failure to deliver pain relief.	Mechanical stiffness when advancing the plunger. Elongation stiffness in inflating the diaphragm. Difficulty holding the device. Difficulty seeing the diaphragm collapse	4	2	2	Yes	The syringe body is constructed in line with conventional LOR syringes and a low friction plunger seal will be employed to ensure fluid plunger transmission. The diaphragm will comprise of a bright colour which enhances visibility.	Ethnographic evaluation to be carried out on the final design to ensure an ergonomic solution. Effective material investigation.	Design evaluation. Material selection. Post market surveillance.	4	1	1	n/a
31	C2.29.2	Is the medical device used in an environment where distractions can cause use error?	The medical device will be administered prior to surgical intervention and in obstetrics. The device incurs no additional distractions over existing epidural syringes. The patient should remain still as directed by the physician in line with current practices.	Incorrect localisation of the epidural needle. Neurological injury and or failure to deliver pain relief.	Patient moving during application.	4	2	2	No	No additional risk reduction methods can be applied here. The procedure requires the patient to remain still for a short duration (approx. 5 - 15 seconds) as in current practice. The occurrence of failure owing to disturbance is low.	n/a	n/a	4	2	2	n/a
32	C2.29.3	Does the medical device have connecting parts or accessories?	The device is connected distally to an epidural needle during application. The epidural needle is unchanged from current designs. However there is an exception for the UK market whereby a special connection is required to connect to the epidural needle as described in the patient safety alert NPPSA/2011/PSA001.	Epidural medicine administered by the intravenous route. Intravenous medicine administered by the epidural route. Intravenous medicine administered by the regional anaesthetic route. Regional medicine administered by the intravenous route.	Mis-connection and wrong route errors. The wide use of the Luer connector design enables wrong route patient safety incidents to occur.	4	2	2	Yes	Develop a safe connector designed for spinal and epidural use only.	Design specification to prevent mis-connection and/or wrong route errors.	Design specification during the design phase.	4	1	1	n/a
33	C2.29.4	Does the medical device have a control interface?	The device does not have a control interface	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
34	C2.29.5	Does the medical device display information?	The device comprises a visual indicator that signals when the epidural space has been reached. A hazard may exist whereby it is difficult to see this indicator.	Incorrect epidural localisation.	Difficulty visualising the visual indicator	3	3	2	Yes	Chose a bright, contrasting colour for the diaphragm material to improve visibility	Select a material which allows for apparent discrimination between the inflated and deflated states. Post market surveillance.	Material selection in line with design and operational criteria. Post market surveillance.	3	2	1	n/a
35	C2.29.6	Is the medical device controlled by a menu?	No the device is not controlled by a menu.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
36	C2.29.7	Will the medical device be used by persons with special needs?	No. The device will only be used by trainee/experienced physicians.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
37	C2.29.8	Can the user interface be used to initiate user actions?	No alternative actions may be initiated by the user interface.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
38	C2.30	Does the medical device use an alarm system?	No the device does not use an alarm system.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a

APPENDIX 4 - PRODURAL DFMEA (UNCONTROLLED COPY)

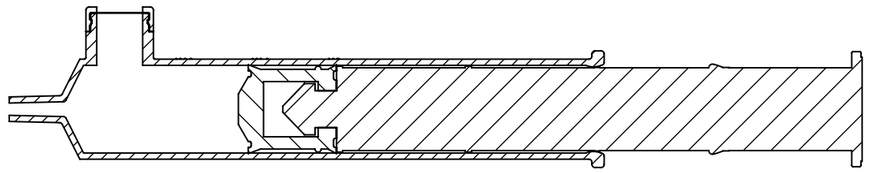
Risk Number	ISO 14971 annex ref. if app.	Source; Component, Function or Standard	Potential Hazard	Clinical Effect	Failure Source	S	O	Risk Level		Risk Reduction Method	Actions for Risk Control	Action taken	S	O	Risk Level	Other Hazards
39	C2.31	In what way(s) might the medical device be deliberately misused?	Inappropriately excessive force may be applied to the plunger causing the diaphragm to rupture due to exorbitant inter-barrel pressure (pressures > 62 kPa). These pressures far exceed current operational parameters. The device may be advanced too quickly not taking account of the haptic and visual feedback.	Severe headaches, pneumocephalus, spinal cord and nerve root compression, subcutaneous emphysema, venous air embolism, and neurological injury	Misuse of the device ignoring best current clinical practices.	4	3	2	Yes	Ensure that best clinical practice is adhered to. Provide operational instructions.	Formulate a training programme which may comprise of physical demonstration and/or teaching videos. Develop an instruction brochure.	Establish training plan. Develop instruction guide. Post market surveillance.	4	1	1	n/a
40	C2.32	Does the medical device hold data critical to patient care?	The medical device does not hold data critical to patient care.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
41	C2.33	Is the medical device intended to be mobile or portable?	The device is a light weight syringe used to locate the epidural space and may be carried and used in the user's hand. The device may fall during application.	Contamination of the device prior to use leading to subsequent clinical complications such as infection.	Device falling or spilling to the ground or to a dirty surface.	3	3	2	Yes	Instruct the end user to dispose of the device and retrieve a sterile alternative. Follow current sterility practices.	Maintain best current practices. Current sterile techniques will not be amended.	Instruct end users to maintain current best practices in sterility	3	1	1	n/a
42	C2.34	Does the use of the medical device depend on essential performance?	The effectiveness of the medical device depends on the proficiency and skill of the physician. The advancements made in this device over preceding technologies should enhance the operational accuracy and effectiveness of epidural administration.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
43	Annex E, Table E.1 A. Energy Hazards	Line Voltage	Line Voltage has no effect.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
44		Leakage Current	Leakage Current has no effect.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
45		Electric Fields	Electric Field has no effect.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
46		Magnetic Fields	Magnetic Field has no effect.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
47		Ionizing radiation	Ionizing radiation has no effect.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
48		Non-ionizing radiation	Non-ionizing radiation has no effect.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
49		High temperature	High temperature has no effect.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
50		Low temperature	Low temperature has no effect.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
51		Gravity	Gravity has no effect.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
52		Vibration	Vibration has no effect.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
53		Stored energy	Stored energy has no effect.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
54		Moving parts	Breakage of moving parts such as the plunger seal and the plunger. Diaphragm securing cap may get dislodged.	Poor performance. Unable to use as intended.	Manufacturing error. Damage during transportation. Misuse.	2	2	1	Yes	Establish quality controls ensuring compliance in product manufacturing. Ensure a good quality shipping contractor. Instruct end user to dispose of any device with visible evidence of misuse and or damage. Develop training programme for end users to demonstrate correct action for use.	Establish a QA system. Employ a reputable logistics company. Label device indicating disposal if damage is visible. Post market surveillance. Provide adequate training programme.	Establish a QA system. Employ a reputable logistics company. Label device indicating disposal if damage is visible. Post market surveillance.	2	1	0	n/a
55		Torsion, shear and tensile force	Potential damage to the device is excess torsion, shear and or tensile force is exerted.	Poor performance. Unable to use for intended application.	Damage during transport. Misuse.	2	1	0	No	n/a	n/a	n/a	2	1	0	n/a
56		Moving and positioning of patient	The patient should be positioned in accordance with best current practices. No deviation from current positioning practice should be observed.	There is little clinical risk associated with the patients position. The clinician will decide if the patient is to assume the lateral or sitting position as with current practice.	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
57		Acoustic energy	Acoustic energy has no effect.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
58		High pressure fluid injection	High pressure injection of the inter-barrel fluid into the epidural can reduce the effectiveness of subsequent drug infusion. However may aid in distribution of anaesthesia if the inter-barrel fluid is saline	Reduction in effectiveness of the epidural anaesthesia	Excessive force applied to the syringe plunger leading to high inter-barrel pressure during fluid injection.	2	3	1	Yes	Maintain current interventional best practice.	Maintain current interventional best practice.	Post market surveillance.	2	2	1	n/a
59		Other issues	No other energy hazard	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
60	Annex E, Table E.1 B. Biological and Chemical Hazards	Bacteria	Bacteria may grow in device.	May cause infection if not sterile. Spinal abscess may occur if bacteria enter the epidural space, left untreated may cause paralysis and incontinence.	Device not manufactured in a clean room. Sterilisation not effective. Device damaged in storage or in transport.	3	2	1	Yes	Employ proper sterile techniques using gloves and anti-septic skin preparation. Ensure the device has been effectively sterilised and packaging remains intact prior to administration. Assemble device in a clean room environment.	Maintain best current practices. Current sterile techniques will not be amended. Ensure quality control during the manufacturing and transport processes.	Instruct end users to maintain current best practices in sterility. Establish QMS to control manufacturing, sterilisation, storage and transportation of medical device.	3	1	1	n/a
61		Viruses	A virus may be passed from one patient to another if device is reused.	Cross contamination. Virus transferred from one patient to the next.	Reuse of device. Device not sterile.	4	3	2	Yes	The device design includes a clip which has to be removed prior to each use indicating that the device has not been used before.	Design specification to include an indicator to signal that it is the first time the device has been used.	Design specification during the design phase.	4	1	1	n/a
62		Other agents (e.g. prions)	Potential of allergic reaction to proteins contained in natural latex rubber or other polymers.	Allergic reaction to non biocompatible material.	Non-medical grade material chosen in the design. Non conformity to biological evaluation.	3	2	1	Yes	Carry out biological evaluation during design stage to ensure that all materials are compatible	Biological evaluation.	Biological evaluation during design stage.	3	1	1	n/a
63		Re- or cross-infection	Re- or cross-infection may occur from one patient to another if device is reused.	Cross contamination. Virus/infection/disease transferred from one patient to the next.	Reuse of device. Device not sterile.	4	3	2	Yes	The device design includes a clip which has to be removed prior to each use indicating that the device has not been used before.	Design specification to include an indicator to signal that it is the first time the device has been used.	Design specification during the design phase.	4	1	1	n/a
64		Exposure of airways, tissues, environment or property	Residues left over from sterilisation process. Air born contaminates. These hazards are presently experienced in conventional epidural administration.	Risk of introducing infection, bacteria or toxic particle into the epidural/spinal area.	Poor sterilisation technique. Corruption of device packaging integrity. Misuse. Spill onto a dirty surface	3	2	1	Yes	Establish quality controls ensuring compliance in product manufacturing. Compliance with best sterility practices within the hospital environment.	Product manufacturing and sterilisation control.	Establish a QA system. Post market surveillance.	3	1	1	n/a
65		Toxicity of chemical constituents	Ethylene oxide used in the sterilisation process is regarded as a toxic agent and should be completely cleansed from the device subsequent to sterilisation. Refer to risk number 14. Potential of allergic reaction due to proteins in certain polymers (refer to risk number 4).	Irritant and known carcinogen. Exposure is very limited. Allergic reaction to device construction material.	Incorrect sterilisation technique not in line with international standards such as ISO 11135. Non biocompatible material.	4	2	2	Yes	Document the sterilisation requirements in line with best international practice and ensure a quality control regime is employed during the sterilisation process. Biological evaluation. Careful material selection in design stage.	Continual product manufacturing quality controls. Post market surveillance. Biological evaluation.	Establish a QMS. Biological evaluation at design stage.	4	1	1	n/a
66		Other issues	No other biological hazard	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
67	able E.1 al Hazards	Incorrect or inappropriate output or functionality	Incorrect localisation of the epidural space/ natural cavity.	Neurological injury, sever headaches, failure to administer pain relief	Balloon rupture, misuse of device, not following current administration guidelines.	4	4	3	Yes	Design increases reliability by incorporating a visual indicator to signal when the epidural space has been reached. Design specification to include a robust design. Design validation through mechanical trials.	Detailed design considering clinical need and validation of final design through bench top and pre-clinical trials.	Detailed design specification. Detailed validation.	4	2	2	n/a
68		Incorrect measurement	No measurement is taken with this device.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
69		Erroneous data transfer	No data is transferred with this device.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
70		Loss or deterioration of function	The diaphragm may experience permanent deformation if expanded beyond its yield point. This may only occur if excessive inter-barrel pressure is experienced beyond the current operational parameters.	This may reduce the confidence that the epidural space has been reached.	Misuse of the device. Excessive force being applied to the plunger.	2	3	1	Yes	The visual indicator expands to between 400-600% elongation for an inter-barrel pressure of 13-20 kPa as determined through end user.	Material selection to insure elastic behaviour for greater pressures well in excess of operational forces applied to the plunger.	Design specification and material selection. Post market surveillance.	2	2	1	n/a
71		Attentional failure	Failure to stop advancement of the epidural needle	Accidental Dural puncture, spinal tap.	Device misuse.	4	3	2	Yes	Maintain current interventional best practice.	Maintain current interventional best practice.	Maintain current interventional best practice. Post market surveillance.	4	1	1	n/a
72		Memory failure	As the time taken to use this device is between 10 and 20 seconds, memory failure is not applicable.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a

APPENDIX 4 - PRODURAL DFMEA (UNCONTROLLED COPY)

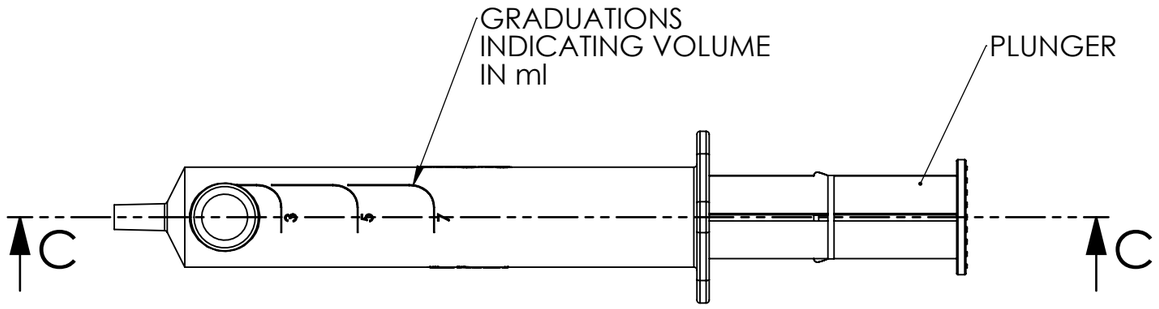
Risk Number	Annex E, T C. Operation	Source; Component, Function or Standard	Potential Hazard	Clinical Effect	Failure Source	S	O	Risk Level		Risk Reduction Method	Actions for Risk Control	Action taken	S	O	Risk Level	Other Hazards
73		Rule-based failure	The physician uses the medical device as intended but has inadequate skill (hand to eye coordination, steady advancement) to accurately determine the epidural space.	Failure to identify epidural space. Failure to administer pain relief.	Inadequate skill levels to carry out procedure.	4	1	1	No	Risk reduction not possible as end user does not obtain the necessary skill level to perform this procedure.	n/a	n/a	4	1	1	n/a
74		Knowledge based failure	The physician may not poses adequate knowledge of the human anatomy to accurately distinguish when the epidural space has been reached. This risk currently exists and has changed with by the use of the presented medical device.	Failure to identify epidural space. Failure to administer pain relief.	Inadequate competency to carry out procedure.	4	1	1	No	n/a	n/a	n/a	4	1	1	n/a
75		Routine violation	Deliberate violation of current epidural administration techniques due to routine disregard for instructions of use is not foreseen.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
76		Other Issues	Skill based mistakes due to inadequate skill level in identifying the epidural space.	Failure to identify epidural space. Failure to administer pain relief.	Inadequate skill levels to carry out procedure.	4	1	1	No	Risk reduction not possible as end user does not possess the necessary skill level to perform this procedure.	n/a	n/a	4	1	1	n/a
77	Annex E. Table E.1 D. Information Hazards	Incomplete instructions for use	Misuse of device.	Failure to identify epidural space. Failure to administer pain relief. Neurological injury.	Incomplete instructions for use	4	1	1	Yes	Establish a QC system ensuring instruction are adequately completed and distributed with packaged device.	Establish QC system	Establish QC system	4	1	1	n/a
78		Inadequate description of performance characteristics	The device may not perform as intended.	Poor performance. Unable to use for intended application.	Inadequate description of performance characteristics	2	2	1	Yes	Design validation and verification post design freeze to ensure device performs as intended.	Design validation and verification.	Design validation and verification.	2	1	0	n/a
79		Inadequate specification of intended use	The device may not perform as intended.	Poor performance. Unable to use for intended application.	Inadequate specification of intended use	2	2	1	Yes	Design validation and verification post design freeze to ensure device performs as intended.	Design validation and verification.	Design validation and verification.	2	1	0	n/a
80		Inadequate disclosure of limitations	The device may not perform as intended.	Poor performance. Unable to use for intended application.	Inadequate disclosure of limitations	2	2	1	Yes	Design validation and verification post design freeze to ensure device performs as intended.	Design validation and verification.	Design validation and verification.	2	1	0	n/a
81		Inadequate specification of accessories to be used with the medical device	The device may not perform as intended. Incorrect epidural needle size may result in unexpected complications.	Poor performance. Unable to use for intended application. Injury as a result of incorrect needle size.	Inadequate specification of accessories to be used with the medical device	3	2	1	Yes	Specify accessories during design stage. Design validation and verification post design freeze to ensure device performs as intended.	Design validation and verification.	Design validation and verification.	2	1	0	n/a
82		Inadequate specification of pre-use checks	The device may be accidently reused.	Cross-contamination	Reuse of device. Inadequate specification of pre-use checks	4	3	2	Yes	The device design includes a clip which has to be removed prior to each use indicating that the device has not been used before.	Design specification to include an indicator to signal that it is the first time the device has been used.	Design specification during the design phase.	4	1	1	n/a
83		Over-complicated operating instructions	This hazard is not applicable owing to the simple nature of this device.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
84		Incomplete warnings of side effects	Incomplete or inadequate warnings of complications due to device misuse.	Clinical complications as discussed previously to possible include neurological injury.	Incomplete or inadequate warning of outcomes due to device misuse. User incompetency.	4	2	2	Yes	Warnings of misuse on device label. Maintain current interventional best practice.	Warnings of misuse on device label. Maintain current interventional best practice.	Warnings of misuse on device label. Maintain current interventional best practice. Post market surveillance.	0	0	N/A	n/a
85		Incomplete warnings of hazards likely with re-use of single-use medical device	This device is a single use device. A virus may be passed from one patient to another if device is reused.	Cross contamination. Virus transferred from one patient to the next.	Incomplete warnings of hazards likely with re-use of single-use medical device	4	3	2	Yes	The device design includes a clip which has to be removed prior to each use indicating that the device has not been used before.	Design specification to include an indicator to signal that it is the first time the device has been used.	Design specification during the design phase.	4	1	1	n/a
86		Inadequate specification of service and maintenance	This device is a single use device. Service and maintenance is not required.	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
87		Other Issues	No other information hazards	n/a	n/a	0	0	N/A	No	n/a	n/a	n/a	0	0	N/A	n/a
88	-							N/A							N/A	
89	-							N/A							N/A	
90	-							N/A							N/A	
91	-							N/A							N/A	
92	-							N/A							N/A	
93	-							N/A							N/A	
94	-							N/A							N/A	
95	-							N/A							N/A	
96	-							N/A							N/A	
97	-							N/A							N/A	
98	-							N/A							N/A	
99	-							N/A							N/A	
100	-							N/A							N/A	

Appendix 5 – ProDural Design Detail

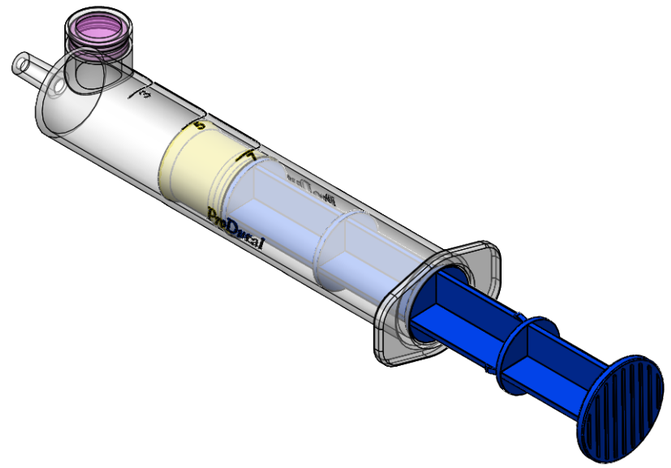
(Uncontrolled Sample)



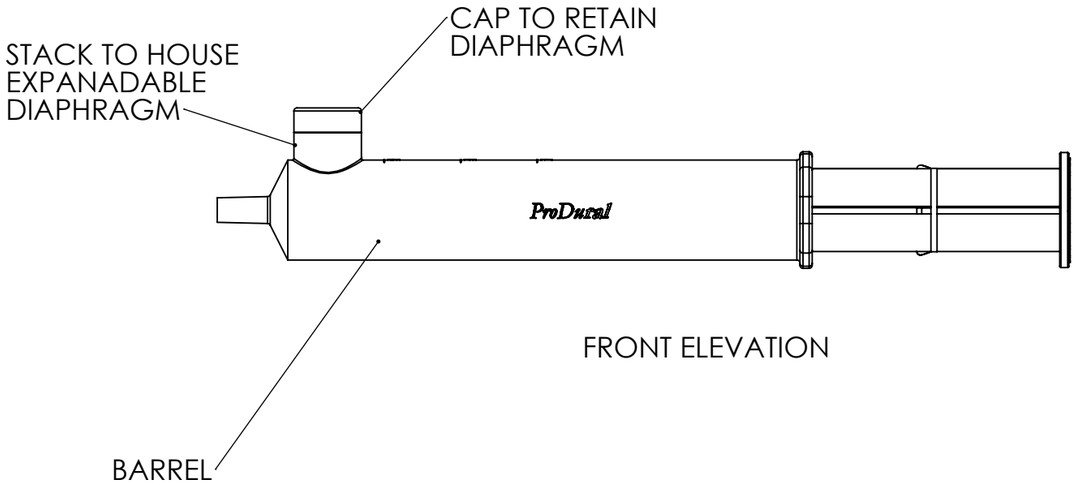
SECTION C-C



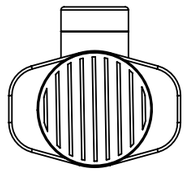
PLAN VIEW



AUXILIARY VIEW

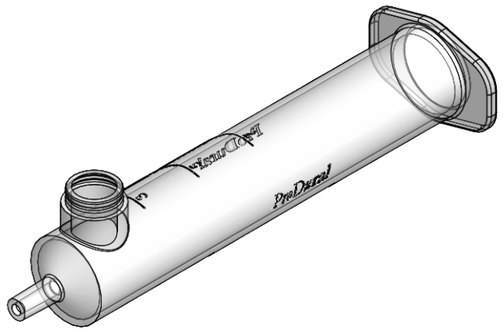


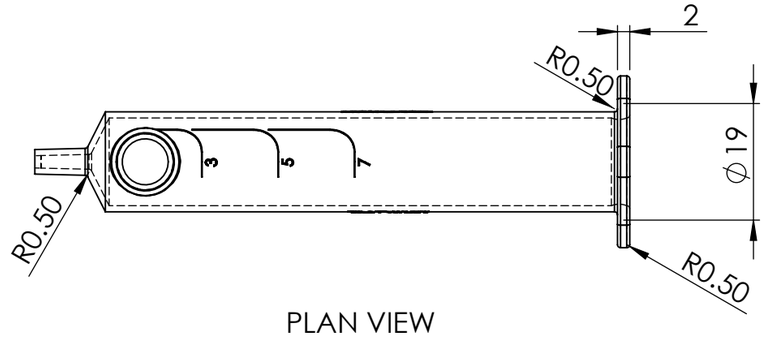
FRONT ELEVATION



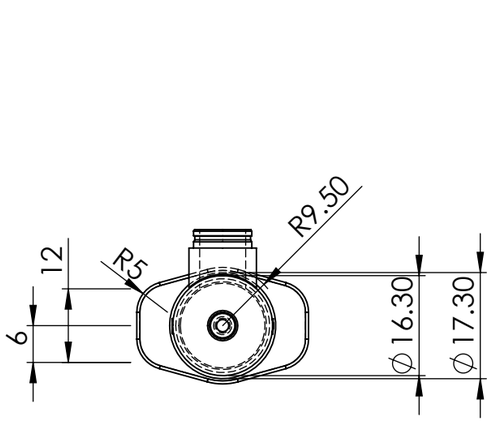
SIDE ELEVATION

UNLESS OTHERWISE SPECIFIED: DIMENSIONS ARE IN MILLIMETERS SURFACE FINISH: TOLERANCES: LINEAR: ANGULAR:	FINISH: INJECTION MOULDED				DEBUR AND BREAK SHARP EDGES	DO NOT SCALE DRAWING / REVISION 1
						UNIVERSITY COLLEGE CORK
	NAME	SIGNATURE	DATE			TITLE: ProDural EpiDural Syringe
DRAWN	CONOR O'SHEA		14/08/2014			
CHK'D						
APPV'D						
MFG						
Q.A				MATERIAL: POLYPROPYLENE, SILICONE		DWG NO ProDural Assembly Ver 3.4 Rev1 / A3
				MASS: 11.14 grams		SCALE:1:1 / SHEET 1 OF 5

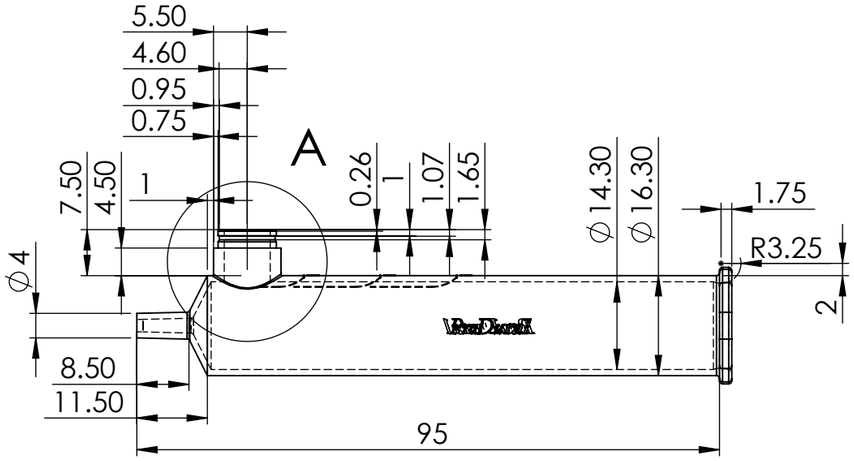




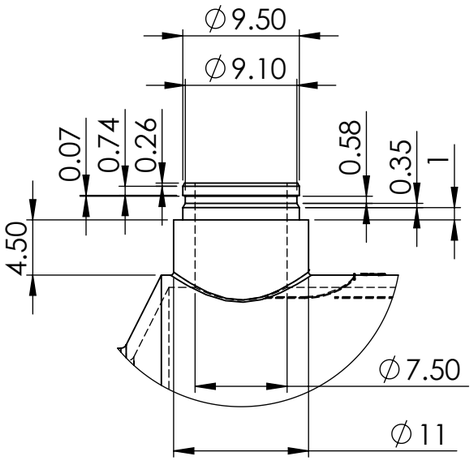
PLAN VIEW



SIDE ELEVATION



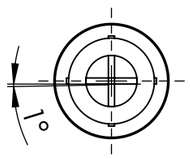
FRONT ELEVATION

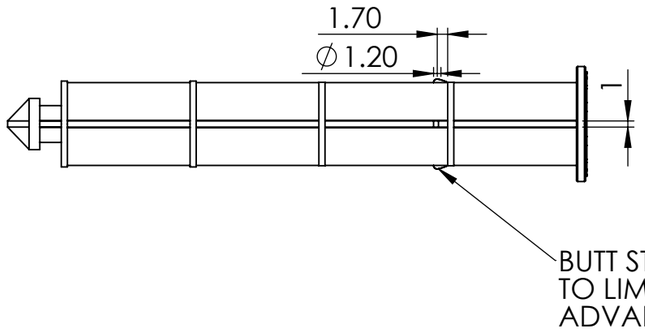


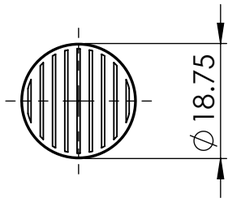
DETAIL A

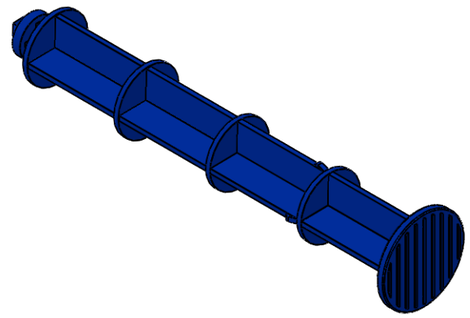
SCALE 2 : 1

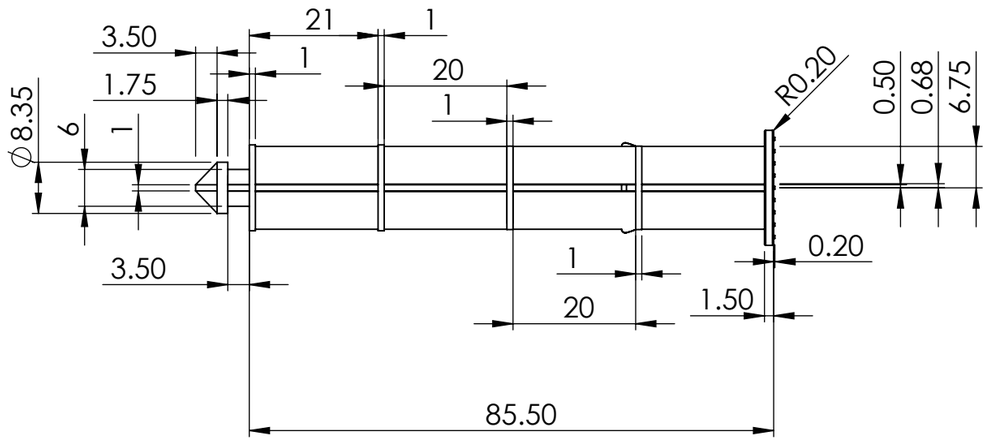
UNLESS OTHERWISE SPECIFIED: DIMENSIONS ARE IN MILLIMETERS SURFACE FINISH: SMOOTH TOLERANCES: +/- 0.1 mm LINEAR: +/- 0.1 mm ANGULAR: +/- 0.5 degrees	FINISH: INJECTION MOULDED TOLERENCE +/- 0.1mm			DEBUR AND BREAK SHARP EDGES	DO NOT SCALE DRAWING	REVISION 1
					UNIVERSITY COLLEGE CORK	
	NAME	SIGNATURE	DATE		TITLE: ProDural EpiDural Syringe	
DRAWN	CONOR O'SHEA		14/08/2014			
CHK'D						
APPV'D						
MFG						
Q.A				MATERIAL: POLYPROPYLENE	DWG NO. SYRINGE BARREL	A3
				Mass: 5.13 grams	SCALE:1:1	SHEET 2 OF 5



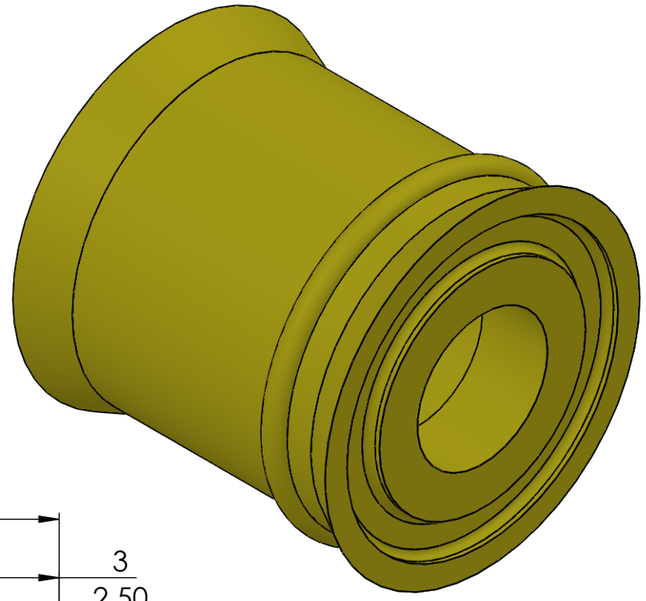


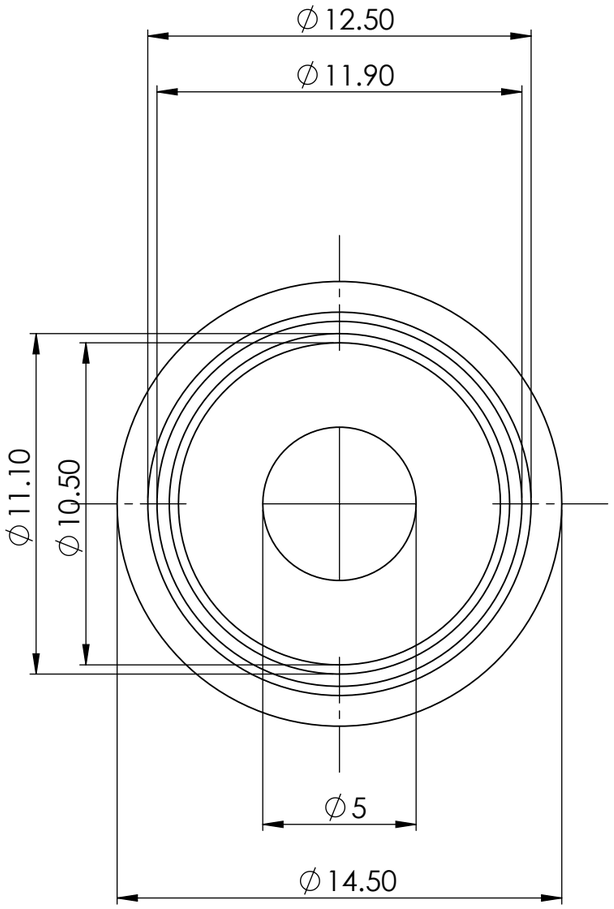


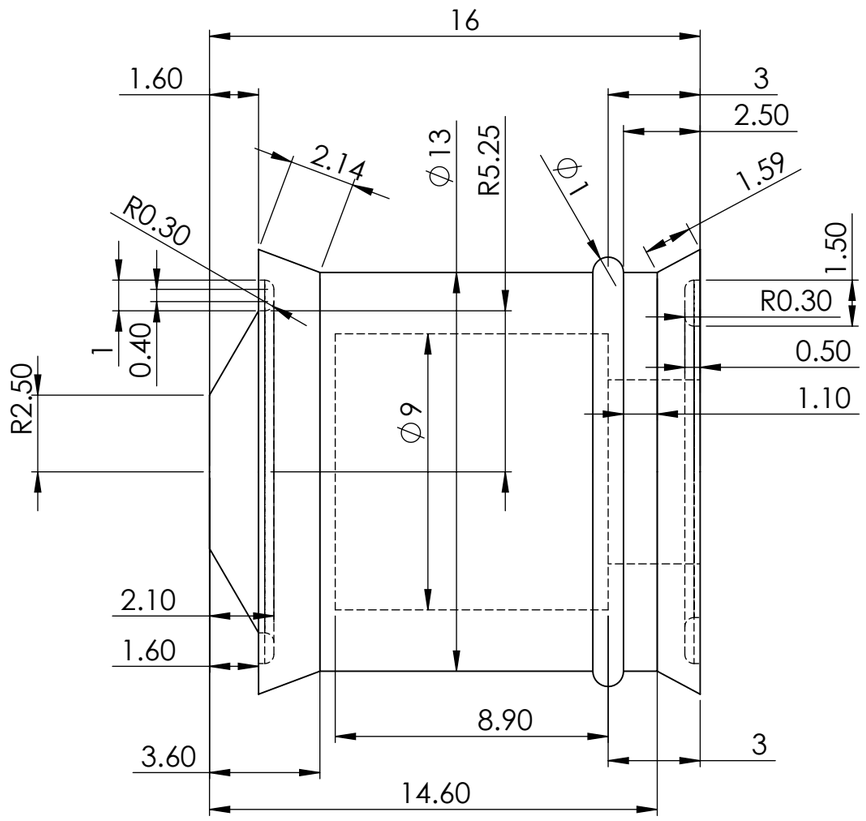


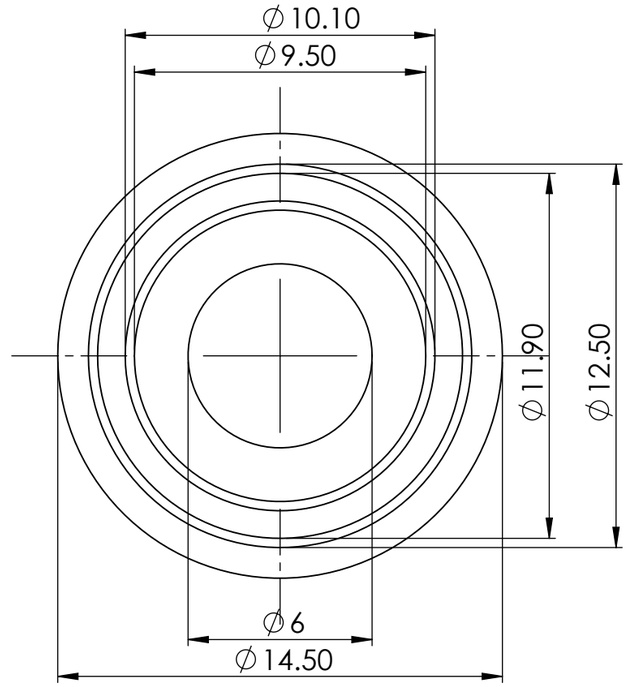


UNLESS OTHERWISE SPECIFIED: DIMENSIONS ARE IN MILLIMETERS SURFACE FINISH: SMOOTH TOLERANCES: +/- 0.1 mm LINEAR: +/- 0.1mm ANGULAR: +/- 0.5 degree		FINISH: INJECTION MOULDING			DEBUR AND BREAK SHARP EDGES		DO NOT SCALE DRAWING REVISION 1
							UNIVERSITY COLLEGE CORK
	NAME	SIGNATURE	DATE				TITLE: ProDural EpiDural Syringe
DRAWN	CONOR O'SHEA		14/08/2014				
CHK'D							
APPV'D							
MFG							
Q.A				MATERIAL: POLYPROPYLENE			DWG NO. SYRINGE PLUNGER A3
				MASS: 3.49 grams			SCALE:1:1 SHEET 3 OF 5

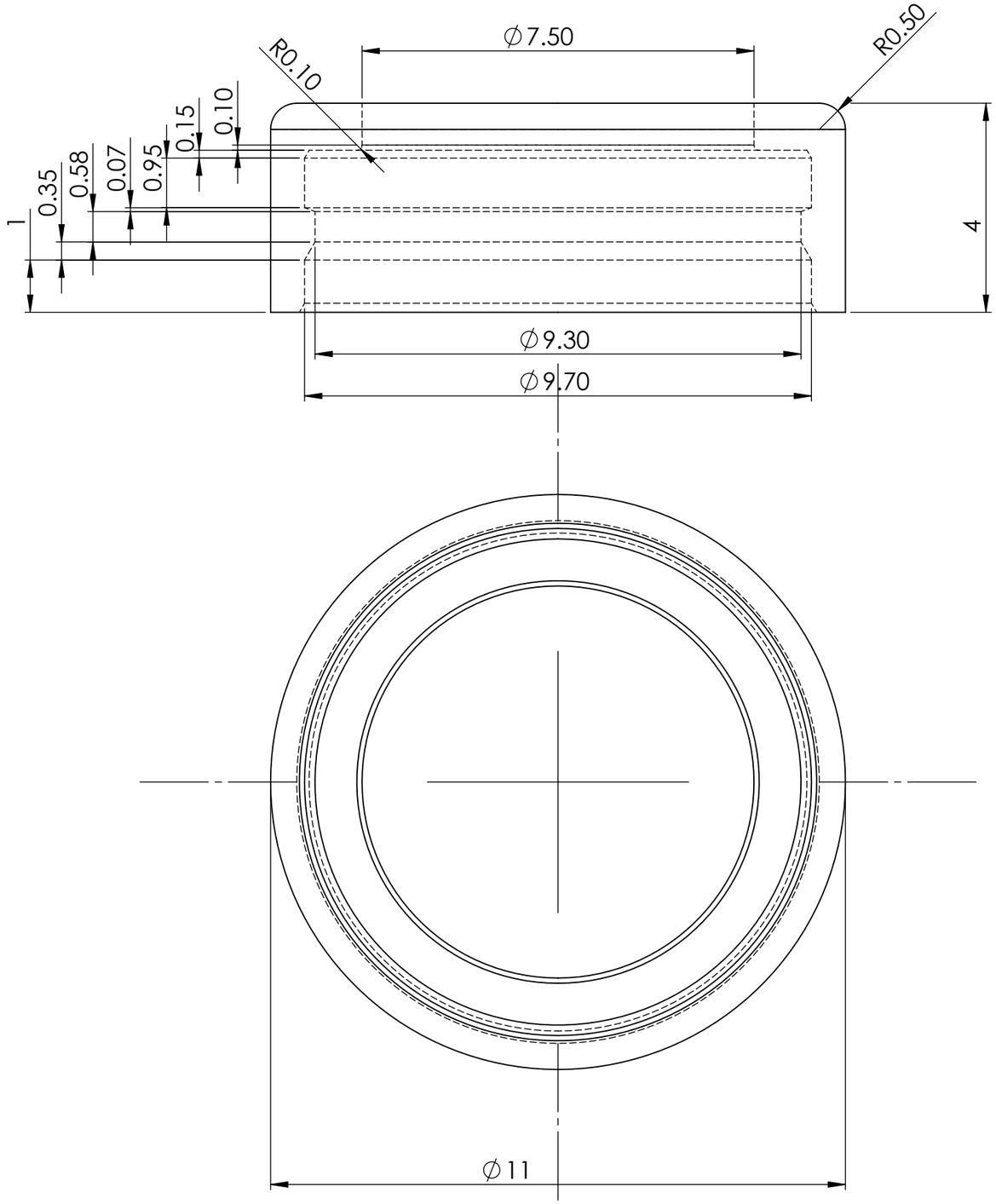


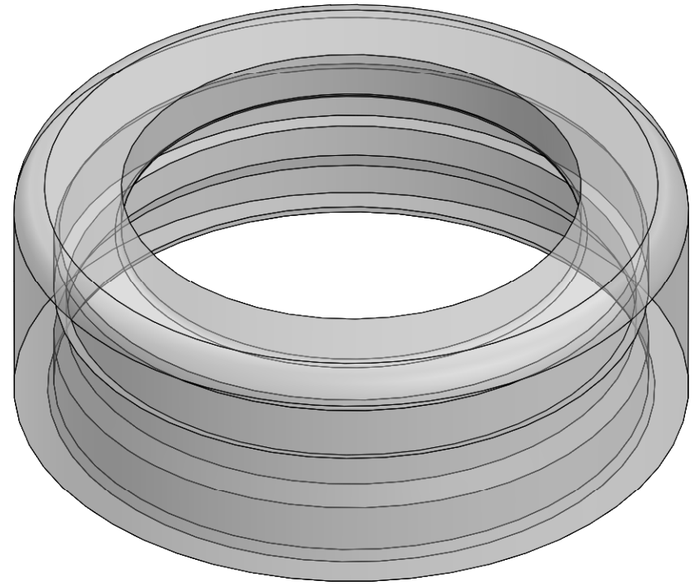






UNLESS OTHERWISE SPECIFIED: DIMENSIONS ARE IN MILLIMETERS SURFACE FINISH: SMOOTH TOLERANCES: +/- 0.1 mm LINEAR: 0.1 mm ANGULAR: 0.5 degrees	FINISH: INJECTION MOULDING			DEBUR AND BREAK SHARP EDGES	DO NOT SCALE DRAWING	REVISION 1
					UNIVERSITY COLLEGE CORK	
	NAME	SIGNATURE	DATE		TITLE: ProDural EpiDural Syringe	
DRAWN	CONOR O'SHEA		14/08/2014			
CHK'D						
APPV'D						
MFG						
Q.A				MATERIAL: SILICONE RUBER	DWG NO. PLUNGER SEAL	A3
				MASS: 1.37 grams	SCALE:5:1	SHEET 4 OF 5





UNLESS OTHERWISE SPECIFIED: DIMENSIONS ARE IN MILLIMETERS SURFACE FINISH: SMOOTH TOLERANCES: 0.1mm LINEAR: 0.1mm ANGULAR: 0.1 degrees		FINISH: INJECTION MOULDING		DEBUR AND BREAK SHARP EDGES	DO NOT SCALE DRAWING	REVISION 1
					UNIVERSITY COLLEGE CORK	
	NAME	SIGNATURE	DATE		TITLE: PRODURAL EPIDURAL SYRINGE	
DRAWN	CONOR O'SHEA		14/08/2014			
CHK'D						
APPV'D						
MFG						
Q.A				MATERIAL: POLYPROPYLENE	DWG NO. DIAPHRAGM CAP	A3
				MASS: 0.11 grams	SCALE:10:1	SHEET 5 OF 5