COMMERCIALISATION FUND PROGRAMME APPLICATION FORM

Applicant & Contributors

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Executive Summary

Understanding the technological aspects of vaccines is essential to comprehending the necessity of vaccinations. Intramuscular vaccinations today provide systemic protection to prime the immune system to combat viruses when they enter the body. The majority of pathogens, however, enter the body through the mouth or nasal cavity. The mucosa, which is the body's initial line of defence and is found in the nasal cavity, works to physically stop pathogens from entering the body while also inducing an immune response that will result in the production of the necessary antibodies to combat the virus. The Naso-Pharynx associated Lymphoid Tissue, the centre of these antibody-producing cells, also resides in the nasal cavity (NALT).

PROBLEM/OPPORTUNITY

There are many issues with the current intra-muscular vaccine route, amongst some:

- Pain – Minor injury at the site of injection can be expected. Along with less common, more serious side effects, which collectively contribute to lowering of patient compliance.
- Muscle fibrosis – This can occur at the site of injection or in the surrounding area. Other potential risks and injuries include hematoma, abscess formation and tissue necrosis.
- Nerve injury – Regardless of the site of injection, all major commonly used sites have some risk of damaging the respective nerve associated with that muscle group.
- Dose Wastage – By far the biggest contributor to this project is to enhance dose sparing by reducing waste and targeting a more viable area for drug absorption.

PROBLEM STATEMENT & SOLUTION

"A way to improve the accuracy of dose deposition of trans-nasal vaccine delivery to reduce waste and vaccinate the population quicker"

Our objective is to design and employ a device that can safely deliver a vaccine to the NALT region in order to increase mucosal immunity. Other gains include a boost in the number of people who can receive immunizations, improved dose sparing via precise and clinical deposition, and improved patient compliance.

MARKET VALIDATION

When discussing the subject of modern vaccination techniques, the market size speaks for itself. In 2019, the market for intra-nasal drug and vaccine delivery was estimated to be worth close to USD 50 billion. By 2020, this market had increased to over USD 53 billion, growing at a steady compound annual growth rate of about 6.5%. Following the enormous spike in disease rates caused by the COVID-19 pandemic in 2020, this rate is anticipated to rise much further during the following few years. Wenting Shu from University College Dublin, Richard Moakes from University of Birmingham, and Eoin O'Cearbhaill from University College Dublin are just a few of the researchers with whom there has been collaborative involvement. These partnerships have guaranteed and reinforced the world's ever-increasing need for a nasal vaccine.

COMPETITIVE ADVANTAGE

- The Nasal Associated Lymphoid Tissue (NALT) in the Nasal Cavity is the target of our vaccine tool. Our device is for targeted distribution to a smaller surface area, which will have higher efficacy due to the presence of Antigen Presenting Cells in the NALT.
- Dose Sparing: To ensure minimal losses inside the channels of the device, the syringe is oriented utilizing gravity while air is also injected into the syringe.
- Using the gold-standard syringes that are readily accessible and the luer-locking adaptor shown in Appendix A, Drawing 1, it is possible to convert from needle base to nasal vaccination immunisation more easily.
- Nozzle design is employed to target the NALT, which was inspired by nasal spray nozzle designs. Adapted design to offer adequate protection for the NALT's surface area.

ECONOMIC BENEFIT TO IRELAND

By providing this design and partnering with manufacturing companies based in Ireland, Ireland will develop as one of the main providers of nasal vaccination devices. This will be a large boost to the medical device industry and pharmaceutical industry.

Technical & Commercial Information

TECHNOLOGY DESCRIPTION

3 - Component Device:

1. Syringe Adaptor:
    - Luer – lock mechanism to twist onto syringes with luer locking female part. Easy attachment and reduced risk of detachment of adaptor.
    - Push-to-connect tubing attachment on opposite side of the adaptor to allow for user to attach easily.
2. Attachable Nozzle:
    - Nozzle with inner teeth, to secure onto outer diameter of tubing. Smooth rounded surface for patient compliance.
    - Nozzle has unique inner channel to produce jet of vaccine to cover specific surface -area of the NALT region.
    - Alternative designs made also for the inner channel to point upwards to prevent solution from entering nasopharynx. Direction of nozzle is decided based on the nasal tubing labelling and positioning.
3. Nasal Tubing:
    - Semi-Rigid Plastic Tubing of about 2 – 1.5 mm outer – inner radius.
    - Nasal tubing to be thermally set to be at angle specified in drawings to ensure a reasonable curvature to navigate the nasal cavity without damaging tissue. Tubing is directed along nasal cavity floor.
    - Green labelling placed on the upper surface to allow for correct positioning of the device.

Scope:

Building on the idea of a substrate added to the current vaccine formulations such as HA and thickening agents. This is to prevent the dripping of the formulation down the nasopharynx and ending up in the upper respiratory tract.

TECHNOLOGY DEVELOPMENT TO DATE

Anatomy background:

To develop our device we first had to understand the anatomy involved. The mucosal immune system acts as a preliminary guard against toxic agents and pathogens from entering the body. It encompasses the largest immune organ in the body and consists of a single layer of epithelium with a mucus outer layer, storing antimicrobial proteins involved with innate and adaptive immune responses. This mucosal immunity can induce systemic immunity and provide rapid protection from pathogens such as Covid-19 which tend to come into contact with the nasal or oral mucosa first and replicate in the upper respiratory tract or nasal cavity.[1][2]

With this in mind we identified the NALT, naso-pharynx associated lymphoid tissue, as the heart of the nasal mucosal immune system due to its high levels of antigen presenting cells that allow lymphocyte proliferation and differentiation following pathogen recognition and set about designing a device to allow this region to be reached and its mucosal immunity activated in a new and innovative way.[3]

Many current nasal vaccines attempt to gain this mucosal immunity by attempting to reach the olfactory bulb and are often inefficient due to difficulty transporting the antigens through the mucosal epithelium and thus larger doses must be used to account for wastage. The NALT circumvents this antigen transportation barrier and thus could be a more effective site with pre-clinical testing in rodents and nonhuman primates showing promising results. [4][5][6]

Prototyping/Testing:

With this goal in mind, we decided on a basic concept of a syringe attachment with a nozzle end to spray/reach the NALT and cover maximum surface area to reduce waste and result in dose sparing.

We completed open chamber testing to investigate the plume of various nozzles on the market to ascertain which would be viable for use in our design by testing their effect at various distances and using this as a guide to determine what is the furthest distance away from the NALT we can position the device.[*Table I*]

Nasal Spray	Area (cm^2) @ 7cm	Comments	Area (cm^2) @ 3cm	Comments2
Otrivine	33.18	Non-unform, omission middle	19.63	Uniform
Betresol	0.79	Circular	0.95	Circular
Nasofan	33.18	Plume, non-unform (tend to middle)	1.77	Plume, uniform
Avamys	12.57	Plume	7.07	No plume
1ml Syringe	7.07	Droplet	7.07	Droplet

Table I – Nasal Spray Test Results

From this we concluded Nasofan nasal spray was optimal for our purpose and resulted in a uniform plume at range of 3 cm and thus we proceeded with designing an apparatus with this nozzle type or similar dimensions in mind.

From research into syringes, we decided on a luer lock mechanism to allow our device to be easily attached to and locked into place and prevent accidental removal when in operation.[7]

A resin model of the nasal cavity was 3-D printed and used for further testing and prototyping. A flexible tube with luer lock and nozzle was attached to a 1mm BD syringe and used inside the nasal cavity model which allowed us to decipher dimensions and effectiveness of prototype plume coverage.

It was found that like the open chamber tests coverage was acceptable 3 cm from the NALT meaning the tube would need to be approximately 4cm into the nasal cavity. A semi-flexible tube of diameter 2 – 1.5 mm was used in this testing to allow it to conform to shape of nasal passage with further tests need to decide optimum material and bend in tube needed with observations from use indicating the greater the bend the more force and/or vertical angel of syringe, (placed upright with plunger pushed downward) , needed to overcome this geometry.

COMMERCIAL OPPORTUNITY/SOLUTION

Our technology seeks to increase the accuracy of intranasally administered (IN) vaccines. Typically, vaccines of all kinds are administered by intramuscular injection (IM), we have identified some critical problems presented by this route of administration. Firstly, up to 90% of patients under the age of 65 report post-vaccination pain [8] and is only tolerated due to the lack of viable substitutes, the knowledge that a procedure is painful typically reduces its use [9] when an alternative is available. Secondly, muscle fibrosis, an inflammatory response that can be induced

by intramuscular injections, decreases muscle function, hinders muscle regeneration after damage and increases muscle vulnerability to re-injury [10][11]. Typically, this is limited to infants, but cases do occur in adults [12][13]. Finally, and most commercially applicably, wastage, there is a large amount of redundant dosage that needs to be manufactured, packaged delivered and injected to amount to absolutely zero immune response. Most recently with covid vaccines, the IM vaccine dose was 30µg within 0.3ml [14] while the IN dose was 0.024 µg within 0.2ml [15]. IN vaccines have had limited success in clinical trials, where they fail to reproduce the same immune response effects as IM vaccines, thus slowing their uptake in the clinic. Our technology addresses this problem by directing the dosage to the main functional tissue of the nasal mucosal immunity system, the Naso-pharynx associated lymphoid tissue (NALT) [16]. Therefore, by advancing our technology to practice, we can resume plans to adopt nasal vaccines in the clinic.

TARGET MARKET

According to the International Forum of Respiratory Societies, lower respiratory infections and pneumonia claim 4 million lives each year[1]. The World Health Organization (WHO) says more than 3 to 5 million people have been hospitalized and 200,000 have died from the flu. Nasal vaccines are emerging as a viable alternative to oral or intramuscular administration due to their non-invasive nature, ease of access, and better immunity. Nasal vaccines protect the mucous membranes of the lungs, reproductive tract, and intestines.[16] Our device has the advantages of accuracy and high efficiency in nasal delivery of vaccines, and will have a broad market in the future.

Before the spread of the Covid-19, there is already a huge market for nasally delivered vaccines. The global intranasal drug and vaccine delivery market size was valued at USD 49.78 billion in 2019. Liquid transfer equipment accounted for the largest market share of 42.8% in 2019 which means that our device has a huge market share. The global nasal vaccines market is growing rapidly with the looming and high risk of viral pandemics and respiratory infections receiving nasal vaccines. Especially to address the Covid-19, although countries have different levels of science and technology, governments of all countries have invested huge sums of money in vaccine research and development. The global intranasal drug and vaccine delivery market size was valued at USD 52.91 billion in 2020. And currently, around 115 vaccine candidates and 155 molecules are in the R&D pipeline. This will further fuel the market growth of our device. It is projected that the global intranasal drug and vaccine delivery market size will be valued at USD 82 billion in 2027 and is projected to grow at a compound annual growth rate (CAGR) of 6.5% from 2020 to 2027.[17]

Espcially, in recent days, Chinese epidemic prevention and control policy has undergone tremendous changes. No longer insisting on the policy of clearing the social aspect, and encouraging people to travel normally, once again put forward a huge demand for vaccines. Especially children and the elderly with low immunity have a huge demand for vaccines. According to the Chinese government, 28 million people over the age of 60 are not vaccinated, about 37 million people have not completed the booster vaccination. Especially with the development of the vaccine, the new nasal vaccine has begun to use, according to Jimu News, the world's first nasal spray COVID-19 vaccine led by Xiamen University was approved for emergency use in China on December 2, and according to news picture (as shown below), our device is very suitable for this batch of vaccines. The device we designed is very similar to the current one, but more advanced. There won’t be the barriers to entry or commercialisation threats. Besides, there are several governments of countries are discussing with China, hoping that China

will import their vaccines, which provides a huge potential market for our device and we can cooperate with these companies/country governments even Chinese government to avoid the huge money for our innovation. To sum up, China is a great target market at present.

COMPETITIVE ANALYSIS

Technology name	Key Features/USP	Strengths/Advantages	Weaknesses/Disadvantages	Other Relevant Information
Your Innovation: NALTOSA	A key feature of this device is the vaccine delivery tube that creates a directed plume towards the NALT region, thereby utilising the administered dose to the maximum.	Directs the vaccine dose directly towards the target region-the NALT, limiting the amount of dose bypassing the nasal mucosa. Easy to administer dose-the same plunging action used to administer Intra-Muscular vaccines is used. Conical nozzle creates a uniform plume of vaccine dose.	Device is more invasive than existing nasal spray vaccines-potentially leading to user discomfort. Additional step of drawing air and vaccine dose into syringe in order to ensure no dose is left in the tubing (to maximise dose sparing).	Device is designed for attachment to a 2.5ml BD syringe. Syringe attachment is reusable, while tubing and nozzle is single use.
Competitor 1: BD Accuspray,	Plunger mechanism on syringe used to deliver vaccine dose, similar to Intra-Muscular vaccine administration Small nozzle, which administers large plume in the form of a 'mist'.	Low degree of penetration into nose-provides more comfortable experience for the user. Pre-filled syringe- reduces steps that a practitioner/pharmacist has to go through in order to administer the vaccine.	Large degree of potential variability in plume direction-making the dose direction highly unrepeatable. Very large plume- increases likelihood of dose bypassing the nasal mucosa and travelling down the gastrointestinal tract The entire device is single use-increasing amount of waste and cost of manufacturing.	Administers Flumist (influenza vaccine for children)
Competitor 2: MAD nasal Atomiser	Soft conical plug seals nostril. The spray atomizes drugs to a fine mist of particles of size between 30 and 100 microns	Atomises vaccine dose in any position- making it easier to use. Simple to use with no sterile technique required. Soft conical plug increases patient comfort and user compliance, while also preventing expulsion of fluid.	High variability in dose direction – increasing chance that vaccine dose travels past the nasal mucosa and into the digestive tract. Dead space in device leads to dose wastage. Syringe must be plunged briskly, otherwise the drug is not atomized but rather 'dripped' into the nasal cavity.	Device used in AstraZeneca trial for the nasal administration of the AstraZeneca COVID-19 vaccine
Competitor 3: Aptar Pharma Nasal Vaccine	Available for liquid and powder formulations.	Low degree of penetration into the nose increases patient comfort. Customizable dose size: can accommodate between 100 and 250mcl. Integrated dose divider allows a second dose to be easily delivered to the other nostril.	Not compatible with standard syringe – whole device must be provided with vaccine dose already installed. Possible high degree of variability in dose direction.	-

Table II – Summary of Competitive Analysis

EXPLOITATION AND ECONOMIC IMPACT

Our product has the capabilities of being both a start-up and an opportunity to licence. As the attachment dimensions of the device can be easily altered, it poses a great opportunity for syringe specific measurements to be adapted. Therefore, a start-up opportunity is very much an applicable option. However, the design can be licensed to medical companies and manufacturers of syringes. Both commercialisation routes are possible, but the intention with our device is to licence the design out to external companies but subject to change relative to revenue opportunities.

The exploitation plan set out of our device is subject to change after final optimisation and testing of the device. Firstly, a patent of the design will be applied for which will give the intellectual rights to the designers. From here a finalised version of the device is to be made and tested, and manufacturing of the product is to begin. Marketing of the device is to be done and the results shown to illustrate the benefits of using our device over the conventional Intramuscular Vaccine. Distribution to hospitals and practitioners is to then commence.

The economic impact in Ireland of our device protrudes to numerous sectors of the medical industry. It is predicted that the use of our device will cut down on the number of healthcare workers that need to be taken away from their daily duties in order to administer Intramuscular Vaccines. Since our device is easy to use and requires no piercings of the skin, a pharmacist will be able to administer which will not only cut down on the cost of extra healthcare staff but also increase the ease of mass vaccination since a patient won't have to travel to a vaccination centre.

FEEDBACK ON YOUR INNOVATION

Contact Details	Details (e.g. summary of meeting notes
Contact Name: Richard Moakes **Company Name/Affiliation: Professor at University of Birmingham** **Date Feedback Obtained: 12/11/2022**	If given the option between a needle and a spray regarding patient compliance, the spray will be preferred. Due to the possibility of a painful spray and the fact that the target site, NALT, is a localized application area, the jet could reduce compliance. By adding thickening agents to change the solution's viscosity, formulation engineering can be used to get around this. For the mRNA vaccine, this can be employed as a solvent. Additionally, to prevent the formulation from drawing moisture from the inner lining of the nasal canal, its osmolarity can be checked. The surface tension can also be monitored at the same time as these data are gathered.
Contact Name: Wenting Shu **Company Name/Affiliation: Mentor at University College Dublin** **Date Feedback Obtained: 28/10/2022**	When it comes to our device's design, there must be minimal waste in the tube and the optimal formulation reaching the NALT because current vaccine delivery devices, such Pfizer's Covid vaccine, have a formulation of 0.3ml. The desired thresholds for spraying out are a formulation base less than 400kda and less than 2%wt. Analysing the user and consumer markets is necessary for ongoing device design improvement. Trypanophobia, or a fear of sharp items in a medical environment, affects 17% of both children and adults. Hence, a large population can be compliant with the device.
Contact Name: Eoin O'Cearbhaill **Company Name/Affiliation: Professor at University College Dublin** **Date Feedback Obtained: 14/10/2022**	Before making a clinical statement, potential issue areas might be identified using GAP analysis. Knowing the present market situation, vaccination adoption rates in various economies, IP laws, and device classifications can help frame a special insight for the device and convey a powerful message to society. FMEA is a good method for identifying the elements that require further focus in order to lower risks of any kind. After conducting an FMEA, minor changes were made to the design to eliminate unnecessary complexities.

Table III – Summary of Innovation Feedback

INNOVATION AND INTELLECTUAL PROPERTY

In an effort to protect our intellectual properties and further develop our innovation, we wish to obtain a patent licensed by the government. This will allow us the sole right to make, use and sell the Naltosa in Ireland for 20 years. It will also prevent others from making, using, offering for sale, selling or importing infringing products in Ireland. The patent will safeguard our design and provide us with legal protection for the external appearance of our prototype, including its distinct shape, configuration, and pattern. As we intend on partnering with already established vaccination companies such as Pfizer and Johnson & Johnson, we plan on filing for a defensive disclosure. This IP strategy will prevent the other party from obtaining a patent on our product.

In order to be granted our patent, we must make sure our design is novel, inventive and has utility. It must be a product that has not been disclosed before and must be reduced to practise under its claims. We had a look into some existing patents relative to our design to ensure nobody else owned patents which our new product might infringe. While we found some patents that had a similar design to our prototype, we were able to highlight unique differences both in its physical outward appearance and in its intended use.

One patent we looked into was a nasal spray with two options of applicator.[18] One port could be used to atomise the liquid medicament in a fine mist to coat the inside of the nose and the second applicator was an ~ 8 cm long flexible tube to dispense the liquid deeper into the nose. Outwardly, this device appeared comparable to our prototype, but the main difference we uncovered was the length of the nasal tube associated with this device was much longer than ours. Due to the accuracy of our adapted nozzle, tests proved that our tube only needed to be extended ~ 4 cm into the nasal cavity in order to dispense the vaccine on our target area, the NALT. This device was also actuated by a generic nasal spray pump while our device relied on actuation by a syringe plunger.

Another patent we considered was a feeding device used for delivering fluid in suspension form to the subject’s airway.[19] Again this device presented similarities to our design appearance wise, however our design again does not extend as far into the nose and instead of targeting the nasal airway, we are aiming for the NALT. There is also no mention of using this device in the field of nasal vaccines, this device is intended for use by patients with neurological disorders such as Alzheimer’s and Parkinson’s disease.

Having contemplated the potential of our model to infringe on the above patents and more, we feel confident that the ingenuity of our device will give us freedom to operate in the desired field of nasal vaccines. Our novel invention can be summarized under the following claims:

1. An adapter for syringe actuated pumping.
2. A thermally heat-set delivery tube which overcomes the external nose and extends ~ 4 cm into the nose.
3. An adapted nozzle to target the specific area of the NALT 3 cm away within the nasal cavity.

Our patent process will first entail filing a priority application in Ireland, which will take about 12 months. Next we will apply for a Patent Cooperation Treaty (PCT) which will assist us seeking patent protection for our invention internationally. From here we can move onto national phase applications where we will ideally commercialize our product all over Europe through the EPO.

APPENDIX

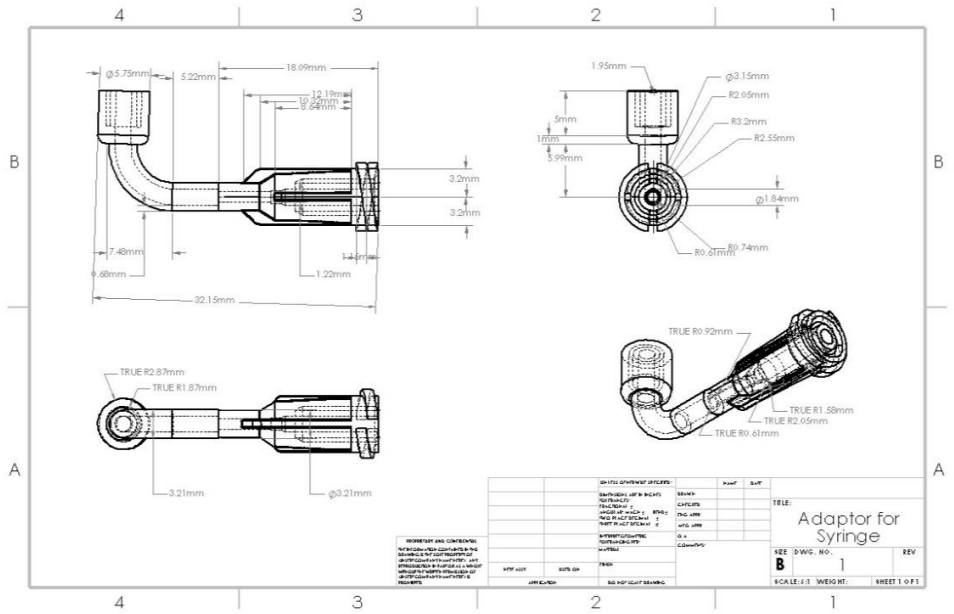

Figure I – Drawing for Component 1: Luer Locking Adaptor for Syringe

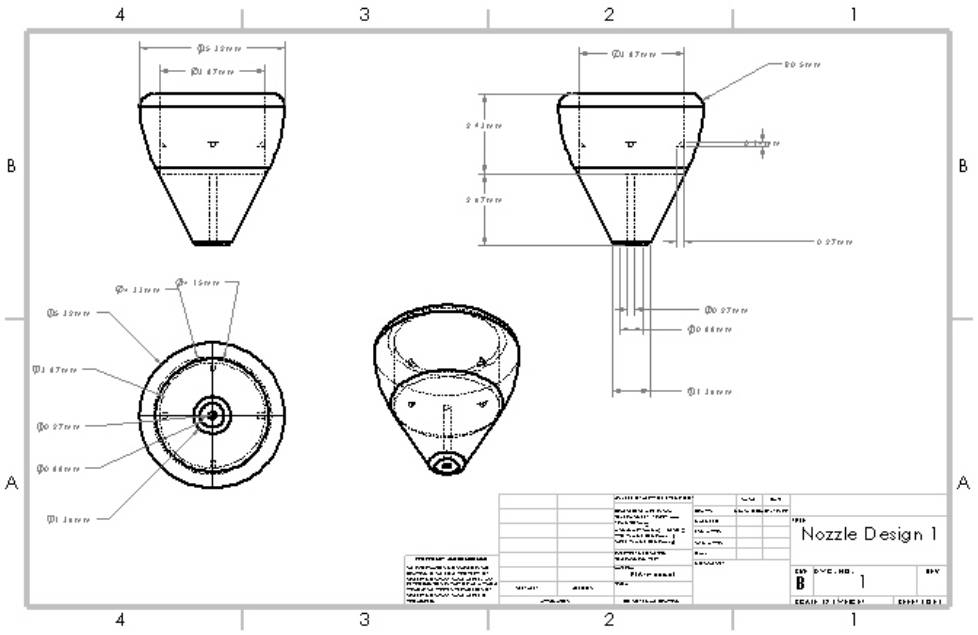

Figure II – Drawing of Component 2: Nozzle Design

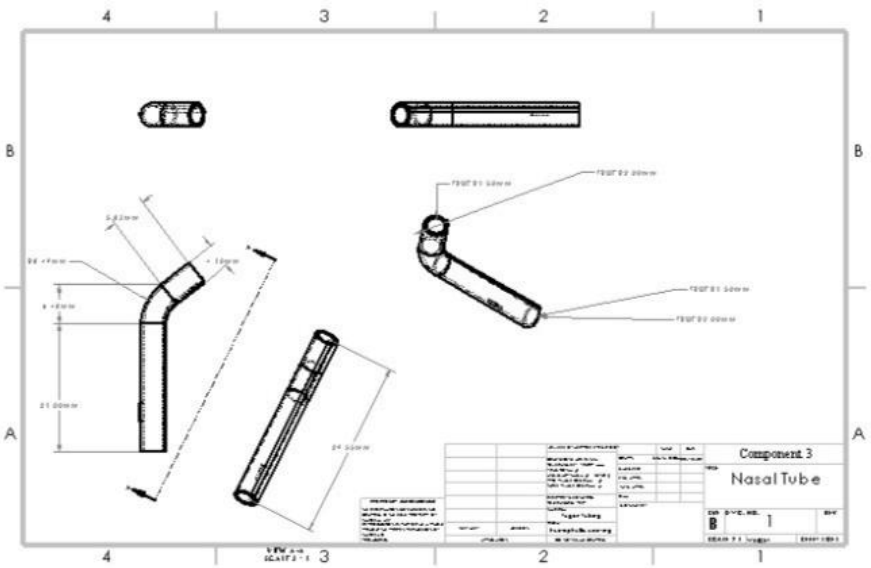

Figure III – Drawing of Component 3: Nasal Tube

Workplan

WORK PACKAGE 1

WP Type:	Technical
Start Date:	M1
End Date:	M6
Manager:	Eoin O'Cearbhaill, Wenting Shu
WP Title:	Material Testing

TASKS

Task Number:	Task Description:
1.1	Tensile Tests
1.2	Test for Biocompatibility
1.3	Material Selection

DELIVERABLES

Deliverable Number:	Description:	Month to be delivered:
1.1	Identify max tension tubing material can withstand	M1
1.2	Identify most biocompatible material in the nasal cavity using In-Vitro methods	M3
1.3	Select material with best results	M5

WORK PLAN

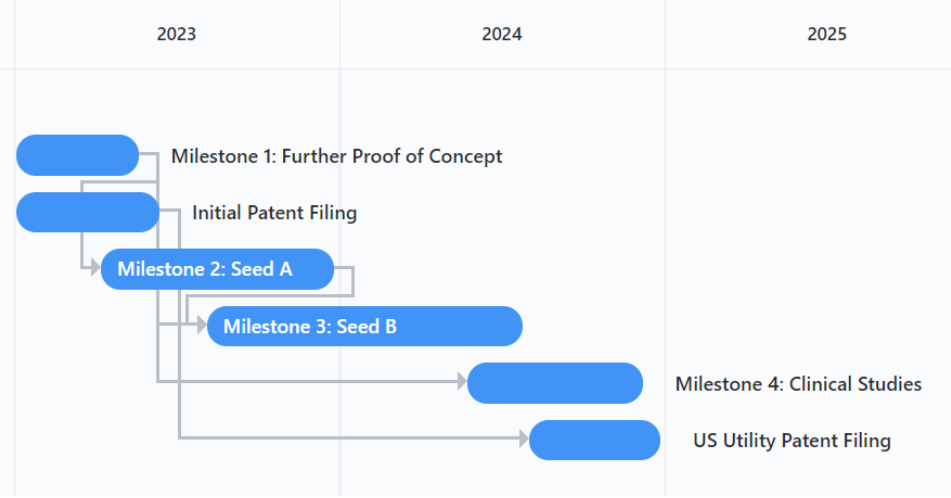

Figure IV – Work Plan

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