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Review

Translation to success of surgical innovation☆

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Summary

Contemporary thoracic and cardiovascular surgery uses extensive equipment and devices to enable its performance. As the specialties develop and new frontiers are crossed, the technology needs to advance in a parallel fashion. Strokes of genius or problem-solving brain-storming may generate great ideas, but the metamorphosis of an idea into a physical functioning tool requires a lot more than just a thinking process. A modern surgical device is the end-point of a sophisticated, complicated and potentially treacherous route, which incorporates new skills and knowledge acquisition. Processes including technology transfer, commercialisation, corporate and product development, intellectual property and regulatory routes all play pivotal roles in this voyage. Many good ideas may fall by the wayside for a multitude of reasons as they may not be marketable or may be badly marketed. In this article, we attempt to illuminate the components required in the process of surgical innovation, which we believe must remain in the remit of the modern-day thoracic and cardiovascular surgeon.

Keywords: Innovation; Intellectual property; Commerce; Industry; Technology transfer; Cardiac surgical procedures

1. Introduction

Thoracic and cardiovascular surgery has developed into prevailing disciplines that use the best products that contemporary technology can offer. Historically, operations have been limited by the equipment availability of their era. There was a limit to how much could be done with a scalpel and a pair of forceps. Technological evolution and surgical progress are therefore inextricably linked, with surgery being the more dependent partner in the symbiotic relationship.

The expectations on today's surgeons have intensified exponentially. The contemporary era is especially challenging in that it has to be transparent in the presence of a much more unforgiving litigious atmosphere. The challenge is to deliver unremitting excellence despite the constant delivery of increasingly challenging surgical substrate, with the expectation of increased service delivery whilst honouring the need to diminish risk [1]. Thoracic and cardiovascular surgeons therefore should be prepared to embrace new technology with open arms to engage the challenges and potentially benefit through the facilitation of health-care innovation [2].

Through this article, we attempt to bring to the attention of innovative surgeons and health-care professionals, the aspects and factors we consider vital in turning good ideas into reality. The main issues that we attempt to cover include pertinent intellectual property (IP) and protection issues, financing dilemmas, commercialisation, strategic plans for idea conversion to product manufacture and regulatory routes. The domains discussed are complex and this article intends to deliver only a simplified overview. We accept that much of the information presented applies generically to all 'medical devices', which include all surgical devices. Where possible we have filtered the information and attempted to restrict descriptions to be specifically relevant to aspects of surgical innovation. We have no expectations that inventive minds will take on future innovative development sole-handed but we hope that this information will make them aware of and help them to harness and use established resources.

2. Innovation: definitions, drivers and hold-ups

Innovation is a complex term, and it is important to understand exactly what is inferred in its use. The differences between discovery, invention and innovation

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must be highlighted. They are basically a function of time. Invention is the occurrence of the idea or *de novo* discovery of a phenomenon, and discovery is the introduction of new fields of practice [2–5]. Innovation follows and describes research that contributes to an already existing field, the attempt to carry it out in practice, the development of novel practice or provision of an alternative solution through the introduction of new elements to what is already established [1–5]. The basic stages which constitute this process are invention, innovation and commercialisation [2].

There are many reasons to justify surgeons' endorsement of this subject area [6]. Ideally, the purpose of innovation should be to enable the introduction of contemporary technology to advance clinical practice facilitating the delivery of optimised health care to the population. It should be the means by which an innovative person can implement good ideas, designed to introduce improvements. In reality, it is the interface with the world of finance and the potential in this area that accounts for one of the strongest drivers of innovation, not in terms of 'why it should exist' but in terms of 'why it *does* exist'. At an international level, surgical and academic innovations generate massive revenue. It is those ideas that generate currency, which attract investment and are more likely to get developed. The corollary is that ideas which do not generate currency are less likely to get off the ground. Therefore, it would appear that financial ramifications are the drivers of innovation. In this way, financial drive can contribute to global health care and, as a surrogate result, fulfils the ethical intention of innovation. Without this inevitable financial association, it could be argued that innovation would experience major inertia issues and falter early, ultimately compromising medical progress.

Aside from the improvement of health care and revenue generation, which can be royalty income or increasing institutional resources, the introduction of new devices offers several other important opportunities, global extension of a surgeon's impact, intellectual stimulation, academic promotion and the creation of an enduring legacy [7].

Having established why innovation should and does exist, the fact remains that its introduction is not always a smooth operation. The professional environment is not necessarily optimally setup to enable surgeons to get involved, especially when they may be dealing with an imbalance of increased workload and decreased reimbursement. Furthermore, a counterweight to the enthusiasm for adopting novelty is the justified tendency to avoid unnecessary risk, and this may slow the unmitigated implementation of innovation [6]. We aim to facilitate this process through the provision of essential information to potential innovators.

3. Innovation, surgeons and ideas

It is worth considering two important issues: the generation of the idea and who has it. It may be a serendipitous stroke of genius, a 'eureka' moment or the result of a systematic problem-solving approach. What is certain is that surgeons are in the best position to have creative views on surgery and also to spot the 'emerging market' [6]. They encounter unique observational experiences in an environment conducive to innovation [1,4]. Other factors recognised to contribute to the generation of good ideas are the innovator's personality, location, being in the right place at the right time and the ability to make decisions, all of which hopefully are surgical attributes [4,6]. These factors justify why surgeons should be involved in innovation. We propose that surgeons should remain pivotal in the process, and take responsibility in remaining contemporary and study applied surgical innovation.

4. Discussion

4.1. What is a medical device?

According to the federal Food, Drug, and Cosmetic Act (section 2001), a device is 'an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar article that is intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment or prevention of disease [8]'. The term covers a massive spectrum ranging from dressings to the components of a fully kitted robotic operating suite and incorporating everything in between. Much of the information described in this article uses references pertaining to all devices, but we have focussed as much as possible on surgically relevant information.

4.2. Protection: intellectual property and multiple layers of protection

A term introduced by the World Intellectual Property Organization (WIPO) in the 1960s, IP is broadly defined as 'creations of the human mind' and is attached to its own specific legal criteria (Table 1 — Link 1). It is crucial to understand the ramifications of intellectual property rights (IPRs) in the context of surgical innovation and device development since no product can come to market without these. IP is essentially formed by four categories, which may be used in isolation or in combination: patents, trademarks, copyrights and trade secrets — each contributing in different ways to the final protection strategy with diverse IP implications and end-points [9].

Prior to any exposure, a common theme to all IPs is the question of disclosure. Timed disclosure and non-disclosure prior to solid IP protection is paramount for success. In the event of public disclosure, a 1-year grace period exists in the United States to complete a patent application. No such grace period exists in Europe [9]. Furthermore, award of a patent does not make the owner of the IP immune from infringements. On the contrary, patents are challenged, and defending them is expensive, on average, costing $5.3 million United States Dollars (USD) [10].

4.2.1. Trademarks and trade names

Trademarks are defined as 'combinations of words, phrases, symbols or designs that identifies and distinguishes the sources of the goods of one party from those of others' [11]. The United Kingdom Intellectual Property Office (UKIPO) describe the trademark as '...a sign which can

Table 1
Useful links and web-based references.

1	World Intellectual Property Organisation (WIPO) Understanding Intellectual Property: World Intellectual Property Organisation. PDF	http://www.wipo.int/freepublications/en/intproperty/895/wipo_pub_895.pdf
2	United Kingdom Intellectual Property Office (UKIPO)	http://www.ipo.gov.uk/
3	NHS Innovations for London	http://www.nhsinnovationslondon.com/
4	Imperial Innovations	http://www.imperialinnovations.co.uk/index.php
5	Department of Health	http://www.dh.gov.uk/en/index.htm
6	Cabinet Office (on 3rd sector)	http://www.cabinetoffice.gov.uk/the_third_sector.aspx
7	Imperial Innovations Distribution Policy	http://www3.imperial.ac.uk/hr/procedures/support/intellectualpropertyrights
8	MHRA: Medicines & Medical Devices Regulation: What you need to know. PDF	http://www.mhra.gov.uk/home/groups/commsic/documents/websiteresources/con2031677.pdf
9	Global Harmonisation Task Force (GHTF)	http://ghtf.org/
10	Medicines and Healthcare Regulatory Agency (MHRA)	http://www.mhra.gov.uk/home/groups/comms-/documents/websiteresources/con2031677.pdf
11	CE Marking	http://www.cemarking.net/alura_xl_com/alura_xl_com_homepage.php
12	US Food and Drug Administration (FDA)	http://www.fda.gov/cdrh/devadvice/overview.html
13	Quality & Regulatory Associates	http://qrasupport.com/FDA_MED_DEVICE.html#fda_med_device
14	International Organisation for Standardisation (ISO)	http://www.iso.org/iso/home.htm
15	Stanford Biodesign	http://innovation.stanford.edu/bdn/index.jsp

distinguish ... goods and services from those of ... competitors' (Table 1 — Link 2).

The presentation of the trademark is a key issue and is specific to words, logos or their combination. This specificity includes the colour, font, placement and all features of a logo or 'name, slogan, symbol or other indicum ... to distinguish the source ...' (Table 1 — Link 2) [9]. Other types of marks exist (such as service marks, coined marks and arbitrary marks), although these are less relevant to surgical innovation.

To publicise that a claim is being made, trademarks are represented by 'TM' (and services marked by 'SM'). This can occur without registering the mark. If a trademark is registered, it receives the '®' sign in addition. This confers additional benefit in that it strengthens its IP claim [11] (Table 1 — Link 2).

The trademark distinguishes the goods or service, that is, helps the consumer to recognise a product. In addition, trademarks alert the consumer as to the origin of the product in terms of which company or enterprise produces it. Trademarks also deliver a 'guarantee function' in that recognition of a mark may be associated with an impression of reputation, almost like a seal of approval. Finally, the trademark contributes significantly to the product promotion, in terms of its 'appeal function' to the consumer (Table 1 — Link 1). If the trademark is represented, it must be done so in exactly the same manner as that specified by the owner [11].

Trademarks are not automatically ubiquitous. To obtain cover in more than one territory, it is possible to apply for a European community trademark with OHIM (the Office for Harmonisation in the Internal Market (Trade Marks and Designs)) or register through a treaty, for example, the Madrid treaty [11] (Table 1 — Link 2).

In conclusion, advantages of trademarks include establishment of ownership and facilitation of national exclusivity. They add strength to the legal protection and may enable future licensing agreements [11].

4.2.2. Copyrights

Copyright protects 'work' which is 'fixed in a 'tangible form' (NHS Innovations for London) (Table 1 — Link 3). The idea itself is not protected by copyright, but the description is. It is therefore not as relevant in the IP protection issues of medical devices and biotechnology [11]. An official registration system is not required in most parts of the world, including the UK. The copyright is designated by the symbol © and this may be added to the product without any external regulation (Table 1 — Link 2). The protection that copyright affords is from the time of creation until 70 years after the death of the creator [11]. Alternative methods of proof of ownership may be to self-send a sealed envelope containing the description and not opening it on receipt (Table 1 — Link 2).

4.2.3. Trade secrets

Also known as 'know how', the trade secret describes the 'grey area' between the formal documented ingredients and the final dish. It is the art or way of doing things [11]. If IPRs were compared to cookery, the patents, trademarks and copyrights would relate to the utensils and recipe, but the trade secret or 'know how' would relate to how exactly the chef puts all those factors together to end up with the *piéce de résistance*. This is an area of interest because this knowledge can make or break the final product. With it, reproduction of the product becomes possible, without which, the soufflé may flop. Whereas the other forms of IP are documented rigidly and protected in specific fashions, 'know how' is not. It is something that may never be declared, and never formally protected but provides a tier of IP that is essentially free and enduring. The recipe for Coca-Cola is probably the best-known example of this. Like any form of IP, 'know how' can be bought, sold or licensed (Table 1 — Link 3).

We have now described several tiers of potential IP. Their instruction and maintenance is complex and should remain in the realms of patent experts. Cullem describes five key tips to successful IP development. These are to think synergistically, to get professional IP advice early, to appreciate IP leverage potential beyond patents, to do the right deals and to align the efforts [12].

4.3. Translational research and commercialisation

Surgeons become an important but single part of a multifaceted system and certainly cannot convert an idea into a

product unassisted. A multitude of non-surgical specialists are required for different aspects of the development such as engineers, scientists and lawyers, to name a few of them. This process necessitates 'translational research'.

Three types of research are described: basic, clinical and translational. Basic refers to laboratory; clinical to that involving human subjects; and translational bringing bench innovations to the bedside. This classification is with the *proviso* that there may be significant overlap among these distinctions [5]. Further described as the process where 'biologic concepts are expanded to clinical applications', translational research relies on this collaborative understanding between the surgeon, the industry and academic institutions [1].

The importance of a healthy collaborative atmosphere is indispensable. There are not many places where this group effort occurs as part of a systematic organised protocol. An example of where this does work is the established collaborative system of surgical innovation at the Stanford BioDesign Program [13].

Beyond this collaboration, successful translational research also requires at least a degree of commercialisation. Research and product development are costly and commercialisation provides for this. Commercialisation may comprise close collaboration with the financial side of the industry or the surgeons themselves becoming more 'entrepreneurial' [9]. Generally, the ideas come from the surgeon/scientist, but the realisation comes from the industry.

Academia and commercialisation are not natural partners. This inherent conflict must be addressed and resolved to enable successful commercialisation. Traditionally considered a taboo area for clinicians, its avoidance is unrealistic since exclusion of financial reality would soon flaw any health system. This union remains a controversial ethical area and invites multiple conflict of interest quandaries.

In considering commercialisation, it is perhaps the endpoint that reveals its purpose. Whereas academic success is the fulfilment of its objective, the discovery of knowledge, commercial success is measured by the quantity of revenue it generates. The objective of technological development is commercialisation in comparison with academic research, which seeks to publish [13].

Riskin et al. add to these concepts by describing the varied impact of differing technological developments on the commercial world. They describe 'disruptive' versus 'sustaining' technology changes. Disruptive technology 'topples industry leaders' while sustaining technology refers to the changes necessary to remain competitive. A cardiac example of a disruptive technology change was the introduction and consequent impact of percutaneous treatment options on traditional surgical re-vascularisation. The sustaining technology component is illustrated by the introduction of stents to follow through percutaneous coronary angioplasty (PTCA) and keep PTCA active. This classification exists as a result of the varied impact on the market share [6]. Commercialisation is therefore entwined with financial factors and cannot proceed without developed IP [14]. The final steps of commercialisation are completed by successful corporate and product development.

4.4. Technology transfer and ownership

Technology transfer is the 'process of moving the intellectual capital of an institution . . . into the public sector . . . for the financial benefit of investors (and) the academic institution . . .' [15]. This entails a transfer of knowledge from the university to the industry, which covers a spectrum and ranges from patents to 'know how', bearing in mind that the university and industry have different outcome objectives [11].

There are many examples of Technology Transfer Offices, which exist to facilitate bridging of the gap between academia and the industry. This enables provision of expertise in all areas of device development [2], for example, Imperial Innovations (Table 1 — Link 4).

Having described how the system should function, there remain many good ideas which fail to flourish because of a translation failure. Some say this is because of 'failure to understand the next step' and others blame the (surgeon's) inexperience in corporate negotiations and lack of tools to take things further [3,9]. Adopting a more commercial approach facilitates some aspects of the process, but translation is complex and there is 'no such thing as a simple recipe' [3].

4.5. Finance and funding

4.5.1. Global economic impact of innovation

Surgical innovation and equipment development are inseparable from the world of finance. Though justifiably expensive to cover development costs, innovation is capable of generating serious revenue. The enormity of the global economical impact of health innovation is illustrated by the growth seen in the biotech sector.

In the United Kingdom, the government has allocated £207 million pounds sterling for the National Health Service (NHS) Transitional Research and Development (R&D) for 2008—2009 with individual institutions such as the Imperial College receiving allocations of £26 million pounds sterling (Department of Health) (Table 1 — Link 5).

The European Biotech sector alone has tripled in the last 10 years and innovation remains an important economical priority. In Europe, initiatives and strategies have been introduced to facilitate innovational development, for example, the European Union Life Science and Biotechnology strategy launched at the Lisbon summit in 2002 [16].

In the United States, by the late 1990s, the US Food and Drug Administration (FDA) had approved 500 000 medical devices produced by around 23 000 different manufacturers. According to a report published in 1997, the Massachusetts Institute of Technology (MIT) alone generated 4000 companies, which employed 1.1 million employees, amounting to a net of $232 billion USD [2,8]. In 2004, American universities and institutes raised more than $1.39 billion USD and applied for over 10 000 patents [7]. By 2005, the top 10 United States research hospitals received $1.2 billion USD for innovation. It seems that the Bayh-Dole created an expectation in terms of innovation, and the amount of money invested in the industry supports the notion that surgical innovation is essential to surgical progress and remains actively encouraged [2].

4.5.2. Devices, drugs, costs and financial benefits

A significant difference is noted in the financial ramifications of devices and drugs. Whereas the development of a drug costs $800 million to $1 billion USD and usually generates $1–3 billion USD, devices usually cost around $60 million USD and generate annual revenue streams of the order of $50 million USD [17]. The price largely depends on the device in question. 'Start-up' costs to bring devices to market range from about $10 million USD for simple devices (Smart Canula™) to $100 million USD for more complicated devices (transcatheter heart valve). The most complex devices (artificial hearts) cost even more [18–20].

In addition to direct commercial value, innovative research also provides indirect institutional value. This may be in terms of enhancement of reputation, prestige and competitiveness. Inflation of such indirect institutional value itself may lead to potential private philanthropy, and this, in turn, may increase the direct commercial value [5].

4.5.3. If to invest, when to invest: entrance and exit strategies

When investing, the baseline common denominator influencing this decision is to address the balance between the value of the idea versus the cost to market it. This is in the context of remembering that good science does not necessarily imply good business but good business does attract investment [3,17]. In calculating the value of the idea, the concept that this is not static but varies according to its stage in its development process must be remembered.

Evaluation is multi-factorial, and several factors must be considered incorporating a supply–demand analysis. In considering this balance, there are three key factors. First, it is important to consider the 'technology' addressing the problem the technology can solve and whether it is protectable; second, 'market' considerations, which include an assessment of the demand and the competition; and third, the 'economic' balance incorporating deliberation on cost versus time taken to develop/see returns [17].

The decision of when to invest is influenced by a dynamic inter-relationship between three incentivised parties: the surgeon (inventor), the company and the investor. (There are circumstances where the company self-invests.) From the inventor's perspective, funds are required to develop the project inclusive of all factors, such as IPR and prototypes. If a company is created or recruited to manage the project, it is of paramount importance to match the capitalisation stage to the company life cycle [21].

Entrance and exit strategies for investment need to be considered from industrial and inventor's perspectives. It is prudent for these purposes to consider industrial recruitment and investment together.

From the industrial perspective, the best investment policy is to invest, as far as possible, in an entity when it is at its cheapest, without compromising the chances of acquiring it. Stoddard and Danielsen state that the further down the development pathway the idea is, the higher the value. They recommend that the optimal time to invest is just prior to the exponential increase in value, which generally occurs between phase I and II clinical trials [15]. In addition to acquiring more for less, other incentives for early industrial inclusion are that earlier involvement strengthens the industry/investor's IP allotment/control and also feeds the time–pressure constraints that drive the industry [2]. In addition, investors generally prefer quick returns [5].

Early financial (or non-)industrial involvement must be balanced against the inventor/university's perspective. This may be in order to reduce early disclosure risk and also to generate higher returns on investment. In the same way that an investor wants to become involved just prior to an exponential increase in value, for the 'seller', the longer this can be postponed, the more advantageous it is in terms of potential revenue generation [2]. Another aspect is that one type of innovation may be more attractive to one investor than another. Fries refers to the 'perceived' value of a patent, and we relate this to investment incentive where 'beauty is in the eye of the beholder' [11]. In summary, the ideal position for an investor would be to invest in an innovation they like, when the product is cheap, followed by the establishment of a quick return. This must be balanced against the 'needs' of the seller.

4.5.4. Funding sources

There are many potential funding sources and, where possible, it is recommended to use multiple sources rather than depending on a single source [1]. We have classified potential funding sources into four main groups (although some categories may qualify for cross-group entry). They are commercial, educational, governmental and third-sector sources (Fig. 1).

Commercial funds cover several categories. In the first instance, an individual may use personal funds or bank loans, although it is essential to set up 'safety' boundaries in this case [10]. Entrepreneurial support may be recruited through private equity. In general, mature companies are supported in this way but 'speculative promise' is also welcomed in this category [21].

Strategic investors include angel investors, venture capitalists and the industry [1,3,9,10,14,21,22]. Often used to 'jump start' clinical or corporate development, angel investors often invest their own money and are usually friends, relatives and/or entrepreneurs [3,9,21]. 'Angels' who usually invest up to $1 million USD (in this context) are defined as having a net worth higher than $1 million USD with an annual income of more than $200 000 USD for each of the previous 2 years [9].

Larger, further developed projects may qualify for the next tier of investment, the venture capitalists. Recruitment of these investors is more taxing and is competitive [9]. Whereas angel investors invest their own money, venture capitalists invest other people's funds [3]. Recruiting venture capital usually implies that there will be some change in 'ownership' and a degree of loss of control during the process [3,10]. Funding projects valued at $5–10 million USD, venture capitalists are expected to generate returns to their investors within 3–7 years. Similarly to angel investors, they themselves take equity [9,10]. They require rigid business plans and, like angel investors, will have regimented exit strategies [9,10].

Financial support from the industry is another option [1,22]. Sachs summarises from personal experience that there are many advantages to industrial financial collaboration, but he cautions that support can be withdrawn as quickly as it is implemented and that, with such support,

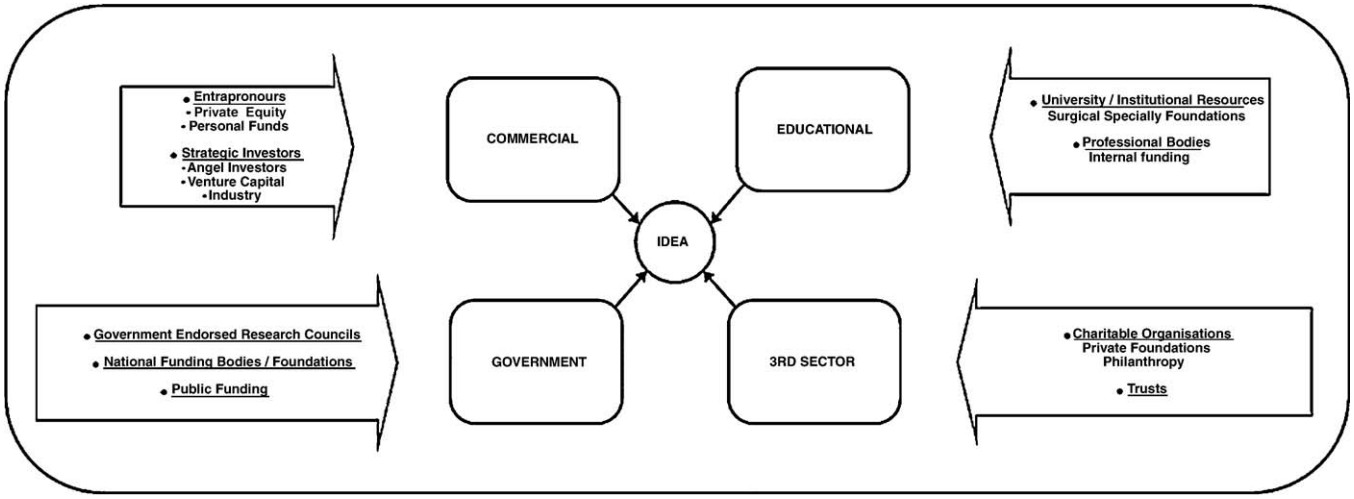

Fig. 1. Potential funding sources for surgical innovation.

several conditions are involved, which may impede disclosure or interfere with publication policies [22].

Government and government-endorsed research councils are also potential serious financial contributors [1,3,9]. These may be an important financial source for 'focussed multi-disciplinary projects' [1]. Examples include the National Institutes of Health, National Institute for Health Research, NHS R&D transitional funding allocations and the Translational Research Council, federal government Small Business Innovation Research and Small Business Technology Transfer Research grants exemplified by projects, such as the Internet, which have originated from federal government-sponsored scientific research [3,9]. Government funding may take time to implement; so for speedier requirements, there may be more of an indication for venture capital input, although this may be at the cost of earlier disclosure [9].

Educational financial sources include university and institutional resources and surgical specialty foundations [1]. Professional bodies may also provide internal funding, such as the 'Innovation Loan Program' or 'Discovery Translational' funds of the Mayo Clinic [15]. At Imperial College, 'Imperial Innovations' provides investment to get ideas going (Table 1 — Link 4).

The third sector is defined by non-governmental value-driven organisations and include the cabinet office (Table 1 — Link 6), charitable trusts, private foundations and all philanthropic sources [1,14].

4.5.5. Generation of capital and licensing

Having discussed options of raising funds to support innovation, we now discuss methods of generating capital. Stoddard and Danielsen describe consulting, know how and licensing agreements [15]. The compensation is usually paid as a royalty, ranging from 1.5% to 8% with an industry average of 3% of net sales [7]. An accepted royalty rate is 25% of the expected pre-tax net profits, although royalty division varies geographically and between trusts [11,23]. The distribution policy also changes according to the cumulative net revenue generated by an idea. For example, at Imperial College, the inventor keeps 100% of the revenue up to a value of the first £50 000 pounds sterling. This percentage progressively drops as the net gain increases with the faculty and college taking increasing shares. When the net value exceeds £500 000 pounds sterling, the inventor's share decreases to 35% (Table 1 — Link 7).

Licensing is governed by licensing agreements, and these enable the process of 'transfer of patent rights from licensor to licensee'. Exact terms must be defined to enable the right to make, use or sell products based on a patented invention. The terms cover the exclusivity of rights, field of use and territory. Furthermore, Fries describes specific financial terms that should be included in licensing agreements. These include technology transfer, access fees and up-front payment, patent prosecution and maintenance fees, milestone payments, royalties, sub-license fees, minimum annual royalties, equity considerations and royalty anti-stacking provision [11]. The licensee pays the patent owner, and the different types of license relate to how much control is given. The different types are exclusive, non-exclusive, sole and partially exclusive [11]. Licensing therefore provides a good alternative to the 'start-up' route since the recruited company organises the commercialisation and forward on the agreed division of royalties [9].

There are, therefore, many different types of investors available, and it is important to select the right type of investor for the right project at the right time.

4.6. From idea to manufacture: innovation models, product and corporate development

The voyage which transforms an idea into a marketable product necessitates the evolution of the device itself (i.e., product development) and of the individuals (and their financial standing) developing it (i.e. corporate development). These components form the two arms of all innovation models. The key to successful corporate development and existence is an organised strategy and robust business plan.

When considering innovation, Heller et al. propose a model based on combining the concepts of Moore and Verloop. This model has three phases: firstly, idea generation and crystallisation, followed by the second phase that is 'development and demonstration of proof of concept'. (This is inclusive of financial consideration and collaborations.) The final phase is 'delivery of innovation to patient care'

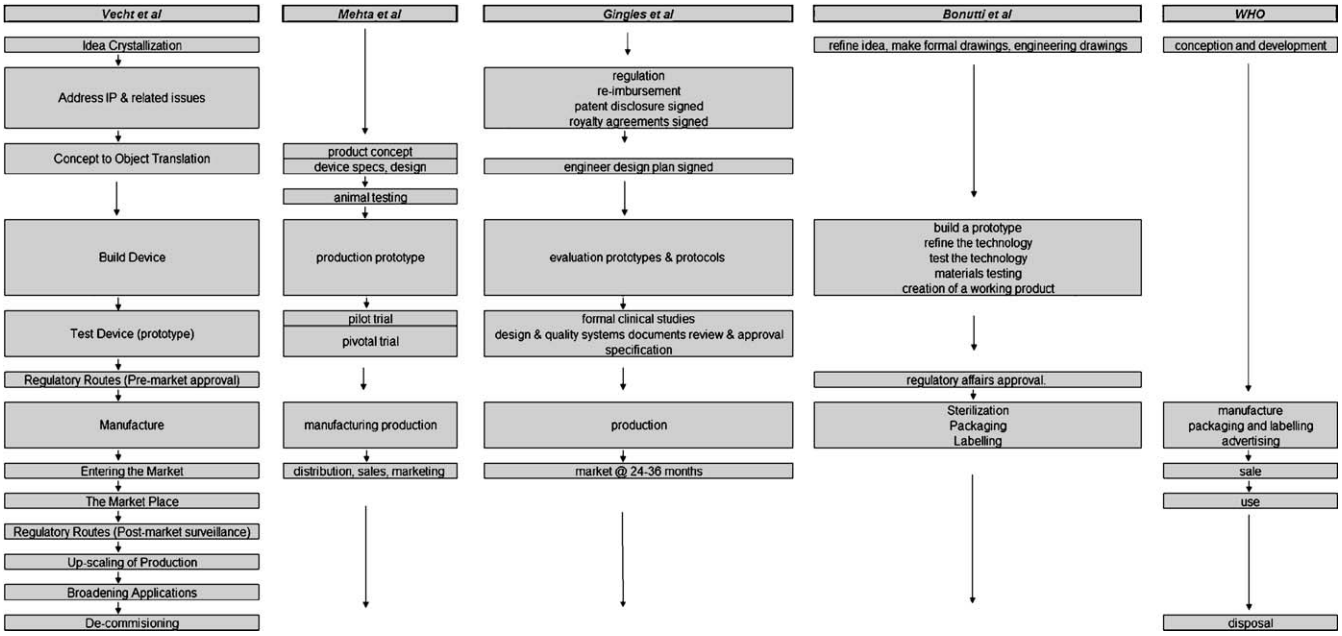

Fig. 2. Summary of product development pathways [7,10,24,25].

[13]. Toner and Tompkins similarly describe 'invention', leading to 'innovation' and finally 'commercialisation' [2].

The corporate and product development processes are inextricably linked with extensive cross-over but, for the purposes of this article, we describe the key elements of the processes separately. Even though the innovation processes are often represented as stepwise sequential steps, in practice, multiple steps should be developed synchronously to enable an overall acceptable product development timeline.

4.6.1. Product development and translational research

Product development describes the process that begins with an idea and culminates with a (licensed), purchasable product. Several product development pathway models are described in the international literature, which describe key elements. In Fig. 2 we have summarised fundamental points, as described by Mehta, Gingles, Bonutti et al. and the World Health Organization (WHO). Using these sources, we have identified common themes enabling us to propose a simplified overview of the device development pathway, and this is represented as shown in the figure [7,10,24,25]. These steps are

1. Idea crystallisation
2. Addressing IP and related issues
3. Concept-to-object translation
4. Build and test device
5. Regulatory routes (pre-market, placing on market, post-market)
6. Manufacture
7. Entering and staying in the marketplace
8. Up-scaling of production
9. Broadening applications
10. De-commissioning

The first stage in development of a device is the idea and its generation. Once an idea is formed, it is important to clarify what type of innovation it will provide since this will influence the choice of the development pathway. Riskin et al. describe two types: enabling and incremental technology. Enabling innovation supports development in a field whereas incremental innovation leads to marginal improvement of already available technology [6].

'Addressing IP and related issues' is the next ongoing stage, which accompanies the device throughout its life. These issues are addressed earlier and in the first part of this series [23].

'Concept-to-object translation' and 'building and testing' the device entails the building of a prototype, which is 'a first or preliminary form from which other forms are developed or copied' [26]. There must be availability of materials and techniques to validate and execute the idea and communication between the 'philosopher and artisan' is essential as is the involvement of those who benefit from the idea through the generation of economic value [2].

To build the prototype, the idea must be refined. Steps include development of formal engineering drawings, materials testing, creation of working product and drawing/design approval by the appropriate regulatory route. The prototype may be built by the inventor, the university and/or specialised companies [10].

Regulation of the manufacture, which occurs before and after market entry, is discussed below.

Manufacture involves specific issues, all of which are regulated. These include aspects such as sterilisation, packaging and labelling [10]. To standardise manufacturing quality, international standards are available, for example, the development of 'Good Manufacturing Practice' (GMP) by the WHO [25].

4.6.2. Corporate development

Following security of disclosure, the first step in corporate development is the decision whether to proceed or not. A good idea, even one promoting patient benefit is not

necessarily marketable since both market and patient factors influence this balance [15]. Bonnutti et al. describe three options available to the surgeon with a good idea. The idea can be presented and surrendered to a medical device company; the surgeon can develop their own IP; or can join a patent licensing firm. They suggest that the last option is the best [10].

Gingles et al. describe two possible routes, the entrepreneurial and corporate partnership routes, and summarise the key steps. For the entrepreneurial model, they describe five steps:

1. Decide company type
2. Register company
3. Construct business plan
4. Raise capital
5. Recruit manager

They describe the following steps for the corporate partnership model [7]:

1. Disclosure agreements
2. Consideration intellectual property
3. Inventor input
4. Development product development pathway
5. Compensation arrangements

Essentially, the key choice is between an entrepreneurial route and some form of corporate partnership [7]. Each route has its own advantages and disadvantages, the discussion of which is beyond the scope of this introductory article. Whichever route is taken, it is almost always necessary to recruit 'external help' since this brings intellectual expertise and money to the table [1].

Having decided upon the route, the inventor is then presented with further decisions. These are: when to recruit help and which exit strategy to adopt. In Fig. 3, we have shown the device development trail centrally leading from idea to manufacture. The academic institution role is shown on the left. The idea may start in the institute or be brought to it, and the extent of time that the institute remains actively involved in the rearing and maintenance of the device is variable. For this reason, the point of academic 'take off' may vary along the pathway, as represented by the two-way arrow. The presence of the academic institute's influence along the trail is in synchrony with the industrial or corporate presence. This is represented by the curved arrow on the right. The point of corporate recruitment is also variable as is the exit point. Again, this is represented by the two-way arrow demonstrating the dynamic interaction between the inventor, the academic institute and the industry or corporate representative.

Another factor influencing the timing of recruiting of external assistance is the current stage of the company. This is especially the case when following the bio-entrepreneurial route. It is also related to financial implications, which

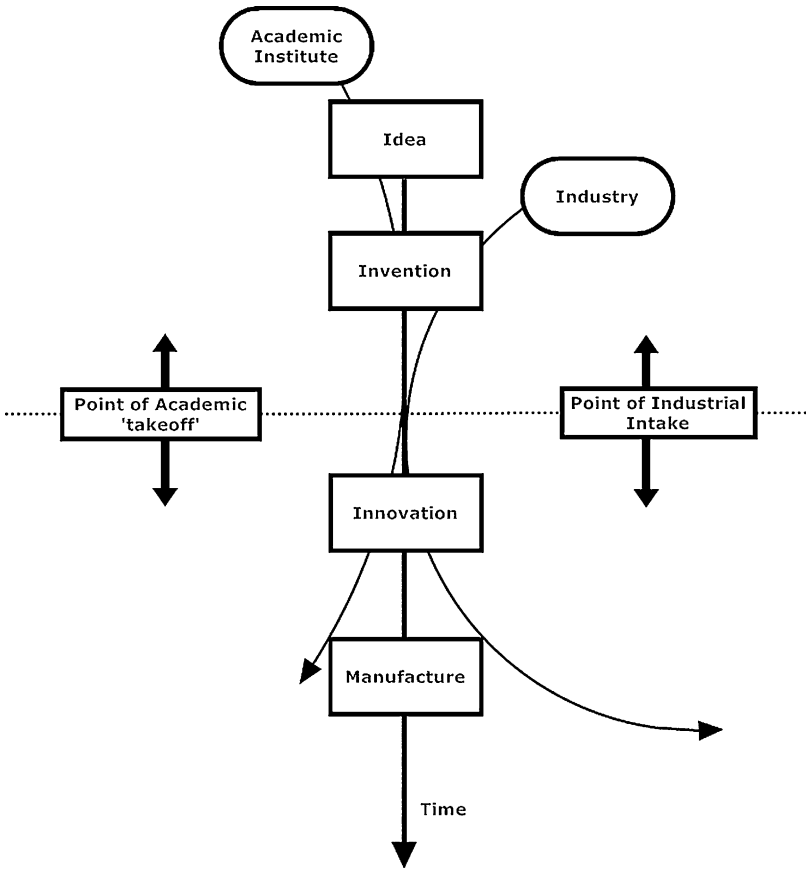

Fig. 3. Dynamic interaction between Academic Institute and Corporate Representative.

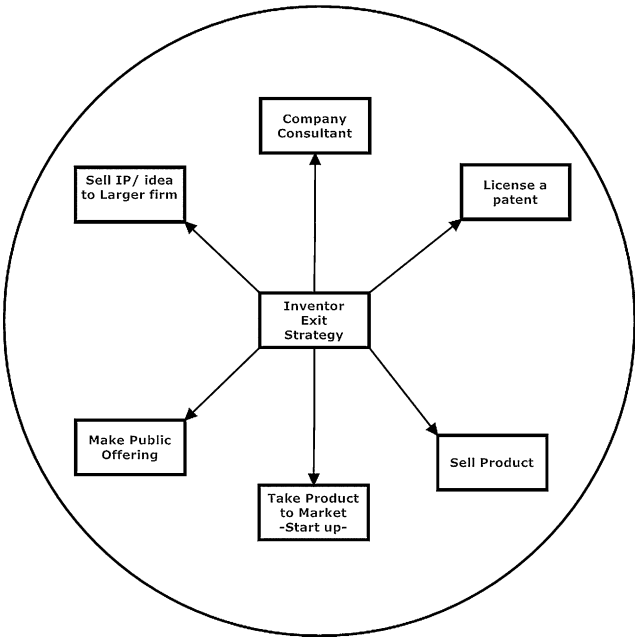

Fig. 4. Inventor's exit strategy based on Bonutti et al. [10].

are discussed separately in the section on financing and funding. Gertler et al. describe four progressive company stages. These are the start-up, early, expansion and later stages. These stages relate directly to the company development timeline, which commences with a conceptual or development phase followed by technology optimisation and pre-testing. This leads to clinical trials and product launch [21].

We have established the need for externalisation; however, a point in time arrives where disunion and separation may be the appropriate next step. We now consider exit strategies for the inventor and the industry. The point of academic/inventor 'hand off' is variable, influenced mostly by the innovation type. There is no 'correct answer' for the best time to disengage. Depending on the invention, the best 'hand off' time may be between invention and innovation [2]. Alternatively, it may be optimal to retain another idea within the academic institute well into the innovation phase, leaving only the 'business execution' to the industry [2]. The point of academic take off does not necessarily coincide with the point of industrial intake since the two may often co-exist until one party takes over. On an individual level, the inventor/institute has several exit strategy options. Bonnutti et al. summarise six exit strategies and we have represented these in Fig. 4. The options are to become a company consultant, to sell the product or idea, license a patent, take the product to market or make a public offering [10].

4.7. Regulatory routes

Once a product development is in progress, risk must be assessed since there are stringent regulations that have to be met prior to the introduction and release of medical devices into the market place and health-care environment.

Regulatory routes are essentially the requirements enforced by individual countries to permit the use of a device in that country. Ultimately, approval from government bodies must be sought, although internal institutional review is often required prior to approaching the national regulator [7]. These territorial-specific routes enable the 'safe translation' of innovative research [5,7]. Different regions exercise distinct routes, although common principles exist.

Regulatory routes are specific to what is being marketed and devices and drugs currently experience different degrees of attention with drugs generally undergoing much more stringent checks [8]. All drugs brought to market must undergo clinical trials whereas this requirement is not reflected in device development. Devices are tested in laboratories and are checked for mechanical and/or electrical safety (Table 1 — Link 8).

Regulatory routes are also specific to the different stages of corporate development. The WHO summarises and describes three stages where government regulation is applied. The stages are pre-market, 'placing on market' and post-market surveillance/vigilance. The pre-market stage controls the product and is the responsibility of the manufacturer. Regulated aspects are the device attributes, manufacturing systems and labelling or representation. 'Placing on market' refers to the sale by the vendor. The regulatory routes here focus on establishment registration and advertising. Finally, post-market surveillance monitors the after-sale by the vendor or user and monitors the product, assessing performance and identifying and alerting problems [25].

There has been an effort to unify regulatory routes on an international level, and this is illustrated by the worldwide initiatives of organisations such as the WHO and the Global Harmonization Task Force (GHTF). They have proposed a universal Medical Device classification system 'according to their perceived hazards', Global Medical Device Nomenclature (GMDN) and promotion of a medical device regulatory model [24] (Table 1 — Link 9).

In both the EU and United States, devices are classified into three classes [25]. The device class represents the risk presented to the patient and the level of regulatory control required [8]. The higher the class, the greater is the potential risk. We will use the United Kingdom as a European example and the American regulatory systems to illustrate these central themes (Fig. 5).

4.7.1. Europe, United Kingdom and CE marking

Since the introduction of the single market in 1992, European countries follow equivalent litigation in this area. The pre-market phase is enforced by a compliance label, which is called a 'CE' mark. The Medicines and Healthcare Regulatory Agency (MHRA) is the active regulatory department of the Department of Health and plays several roles (Table 1 — Link 8).

The pre-marketing role is through the 'appointment and auditing of notified bodies', which are third-party accreditation bodies [27]. In addition, the MHRA monitors adverse events and feeds back this information to the manufacturer. The MHRA is powerful, being empowered to remove products from the market, and plays an active role in education [27].

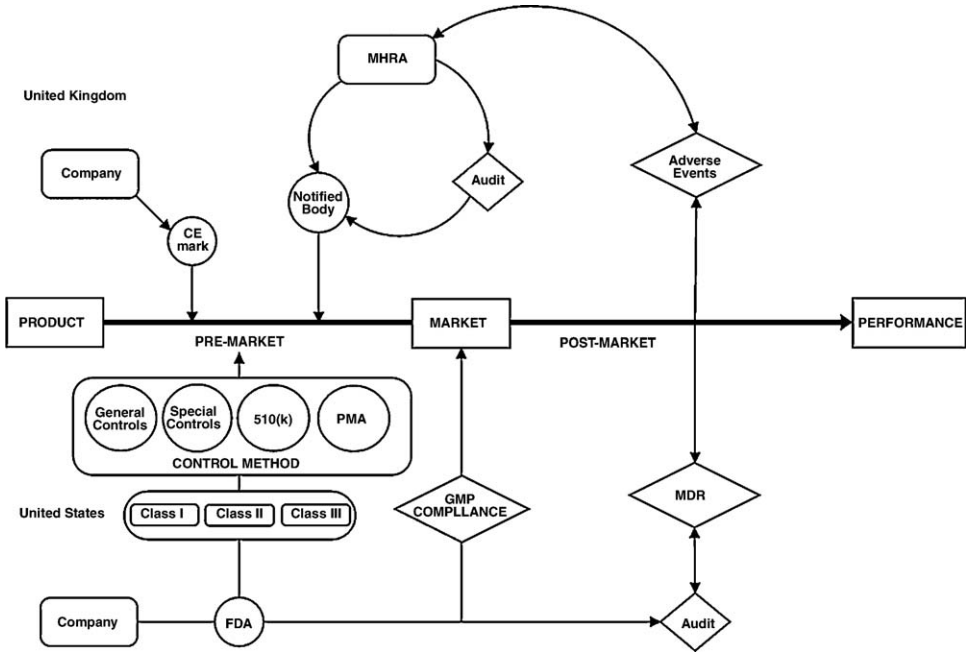

Fig. 5. Regulatory routes: Europe and United States.

The 'placing on market' phase is facilitated through monitoring information on adverts, labels and product information leaflets. (Counterfeit medical devices are also controlled as are products that are not necessarily licensed as medical devices). [Table 1 – Link 8]. The MHRA relies on clinicians and manufacturers reporting to them to enable post-market surveillance, and this is implemented through the adverse incident reporting scheme. They may issue a medical device alert or product alert and can enforce changes in design and disseminated information. Cardiac prosthetic heart valves and annuloplasty rings have been taken off the market by the MHRA (Fig. 5; Table 1 – Link 10).

The CE mark is a mark of compliance using the letters 'CE'. We found very useful online information at 'CEmarking.net' (Table 1 – Link 11). Here, Zuyderwijk gives an online synopsis lecture from which we have derived the following summary. The 'CE mark' should be referred to as 'CE marking' and it is an abbreviation for European Conformity or '*Conformite Européenne*'. Applied by the manufacturer, its presence indicates European safety compliance and enables marketing in specific territories [27]. It is applied by the manufacturer, and without it, in general, a medical device cannot be marketed in Europe (Table 1 – Link 8). These territories are the EU, European Free Trade Association (EFTA) and candidate EU members such as Croatia. (It is noted that Switzerland has a mutual agreement other than CE marking that is considered equivalent.) It is important to emphasise that the mark is not representative of quality. CE marking is obligatory for any product which falls under the remit of the 'New Approach Directives' of the EU. For the purposes of this article and health-care-related appliances, the relevant directives are: Medical Devices (93/42/EEC), Active Implantable Medical Devices (90/385/EEC) and In Vitro Diagnostics (98/79/EEC). In the UK, for anything other than a very low-risk device, the CE mark must be verified by an independent certification body or 'notified body', and these are appointed by the MHRA (Table 1 – Link 8).

Class I devices (excluding those with measuring function or sterility requirements) do not require pre-market approval but must follow basic safety requirements. Other class I, class II and III devices must be submitted to the regulator with 'a declaration of conformity to the appropriate EC directives and details of the conformity assignment assessment procedure followed'. For higher-risk devices, the corresponding EC certificates issued by a notified body must also be submitted to the competent authority [25].

4.7.2. United States

In the United States, regulatory routes are enforced by the US FDA (Table 1 – Link 12). Most of the relevant regulations are found in 'title 21 code of federal regulations (CFR) part 800 to part 1299' [8]. This includes not only specific routes for devices, but also different routes for different devices [17]. As in Europe, class I devices only require basic regulations (or general controls) such as sterility and are exempt from pre-market notification. All device classes are subject to general controls [28]. Higher device classes require more stringent regulation [3,8]. Class II or 'medium-risk' devices require 'special controls' inclusive of labelling requirements, mandatory performance standards, post-market surveillance and FDA guidance. Products are then essentially cleared by one of two routes: pre-market approval (PMA) or through a '510k' marketing clearance. The 510(k) demonstrates 'substantial equivalence to a legally marketed predicate device' and may be necessary for class II devices [7,8,28]. The PMA entitles study of devices in humans and is generally required for class III devices. There are some class III devices covered with a 510(k) [7,8,28].

Feldman et al. state that the majority of device regulation in the US occurs via the 510(k) route [8]. Following 'the

federal medical device user fee and modernisation act of 2002', the FDA is entitled to charge for their regulatory work. PMAs are very expensive (>$3million USD) whereas 510(k) cost less ($10–15 000 USD) [7]. The 510(k) review is quicker to complete (20–90 days) than the PMA clearance, which takes twice as long (180 days) (Quality and Regulatory Associates) (Table 1 – Link 13).

The 'placing on market' phase in the United States requires an 'establishment registration' [25]. This applies to the place where the device is manufactured and costs $1861 USD (Table 1 – Link 12).

4.7.3. Post-market surveillance/vigilance – common routes

The third phase of post-market surveillance/vigilance also incorporates adverse events reporting. In the 1980s, the FDA was criticised for inadequate post-market assessment and, as a result, the Congress introduced the 'safe medical devices act' in 1990, which was amended in 1992 [28]. Common themes and requirements demonstrate global post-market surveillance compliance (as defined by GHTF). The five components of a comprehensive post-market regulatory component include problem reporting, implant registration, distribution records, recall procedure and complaint handling [25]. The FDA lists other basic regulatory requirements that manufacturers must comply with. These are Establishment registration, Good Manufacturing Compliance (GMP), Medical Device Listing, Investigational Device Exemption (IDE) for clinical studies Quality System (QS) regulation, Labelling requirements and Medical Device Reporting (MDR) (Table 1 – Link 12).

Hence there are clear routes, which must be adhered to, that ensure a proposed device is health and safety compliant. Other sources of advice and guidance are available from the International Organization for Standardization, which issues risk management advice to manufacturers (ISO 14971:2000) (Table 1 – Link 14).

4.8. Entering the market place

We have described the key components that constitute a successful idea to product passage. Their implementation requires a well-managed multi-faceted team. This is dependent on selecting the right team and executing the right business plan.

4.8.1. The team

The innovation journey is not one to make alone. Expert advice is necessary for all aspects of development, perhaps with the exception of those in which the inventor feels proficient. Areas to be covered include IP advice, corporate direction, manufacturing expertise, regulatory proficiency and marketing know how [10]. Crucial elements remain sensible disclosure policies and a positive collaborative team environment. Whether progressing your own IP or synergising with a corporation, expertise provision beyond the capability of the academic institution will make the voyage more seamless [2]. Chitwood also points out that this is a great opportunity for surgeons to learn new skills, and advocates interdisciplinary and industrial collaboration [1].

4.8.2. The business plan

The business plan is the way in which the overall plan is implemented, and its construction and explanation is beyond the scope of this article.

4.8.3. Planning and strategy

Getting onto the market requires information dissemination and advertising. This lies within the scope of the marketing team but good scientific analysis and justification will also naturally enhance use and ultimately sales.

It is important to question whether a project can ever really finish or if it remains in an ongoing active cycle. As time progresses, 'new' challenges may impinge on the maintenance and market phase of the product, for example, customer feedback, the availability of new materials and technology, new regulations and new markets. The inventors and their team should be prepared to adapt to the market in which they exist and upgrade, adjust or de-commission as the environment dictates.

4.9. Surgical innovation in real life: ethical considerations in practice and training

Considering surgical innovation according to the four *prima facie* principles of medical ethics (autonomy, beneficence, non-maleficence and justice) enables the construction of a logical framework and raises interesting dilemmas [29]. There are two aspects: the impact of a specific device on a patient/recipient and contemplation of the more generalised philosophical implications of surgical innovation implementation.

Autonomy is essential and, we assume, universally respected. This applies specifically to the scenario of an individual patient/recipient. Depending on the innovation in mind, patients should be fully involved in the decision-making process and where applicable, consent may be required.

Beneficence on an individual patient level has obvious benefits with the scope of improving both prognosis and quality of life. We have extensively discussed the broader beneficial implications of surgical innovation, which are very positive. However, controversies arise when deliberating issues of non-maleficence. On an individual patient basis, there is the issue of possible complications resulting directly from a new device or procedure. This introduces a potential risk, which may have an impact on the mortality and/or morbidity outcome. This must be carefully balanced against the benefits in a considered argument. Thinking beyond the implications affecting an individual patient, it is important to consider the more generalised issues. An important concern is the danger that those involved in innovative development may not be impartial in their judgement. It is inevitable that a conflict of interest is introduced since clinically successful products may lead to personal and institutional monetary gain. Furthermore, if an inventor has personal equity in the product, one may become biased and unobjective in their assessment and management [10]. There may be a concern that the enthusiasm of the inventor or promoter clouds the perception of the actual results,

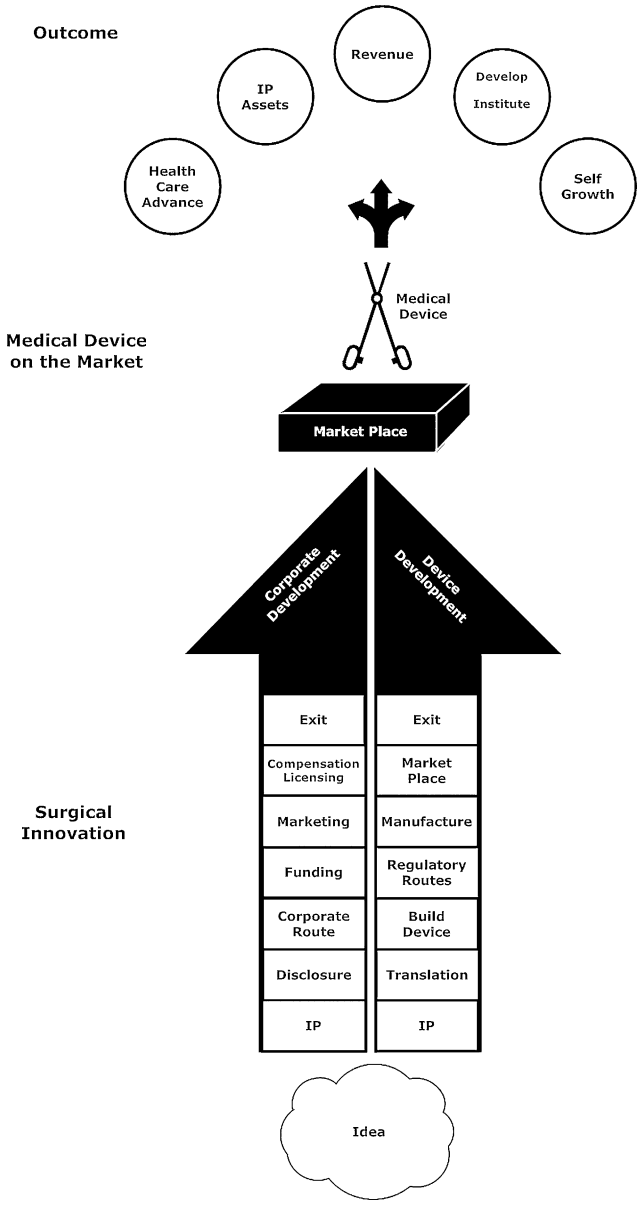

Fig. 6. Overview of surgical innovation.

which may, in turn, could prejudice the appropriateness of developments.

Justice in this scenario is the 'moral obligation to act on the basis of fair adjudication between competing claims' [29]. To assist, there exist clear institutional and governmental policies to prevent and discourage likely conflicts of interest. It is the responsibility of inventors to familiarise themselves with their local and national liability. A specific recommendation is that it is good practice for inventors to use their own devices and not just develop it in the hope that others will use it [7]. Regulatory routes on surgical innovation are stringent, although some would argue that all innovation should be even more tightly audited and monitored through an independent process.

It is our opinion that surgical innovation is an essential prerequisite to keeping thoracic and cardiovascular surgery competitive. This is especially the case in the context of an appropriate global attitude of a need for better results in the presence of less morbidity. This atmosphere probably propels forward non-surgical treatment options so surgical options need to remain attractive, novel and contemporary, and this cannot occur in isolation of innovation. It is essential that surgeons are familiar with the processes and resources available to turn good ideas into realities. The importance of surgical innovation is also ratified by the recent incorporation of IP and innovation training into the surgical curriculum. One of the best international examples is Stanford University where a Surgical and Biodesign programme has been developed (Table 1 — Link 15).

5. Conclusion

We have attempted to provide an overview of the processes involved in the development of a medical device. We have demonstrated that beyond a 'good idea', there are many factors that need to be considered. Bringing together all these components to achieve a safe, marketable device that generates revenue requires skill, knowledge and assistance. Fig. 6 is a schematic representation of our overview of surgical innovation. There is no simple 'quick fix' and as the great American inventor Thomas Alva Edison said, 'Invention is one percent inspiration and ninety nine percent perspiration'.

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