



Review article

Nerve guidance conduit development for primary treatment of peripheral nerve transection injuries: A commercial perspective

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ABSTRACT

Commercial nerve guidance conduits (NGCs) for repair of peripheral nerve discontinuities are of little use in gaps larger than 30 mm, and for smaller gaps they often fail to compete with the autografts that they are designed to replace. While recent research to develop new technologies for use in NGCs has produced many advanced designs with seemingly positive functional outcomes in animal models, these advances have not been translated into viable clinical products. While there have been many detailed reviews of the technologies available for creating NGCs, none of these have focussed on the requirements of the commercialisation process which are vital to ensure the translation of a technology from bench to clinic. Consideration of the factors essential for commercial viability, including regulatory clearance, reimbursement processes, manufacturability and scale up, and quality management early in the design process is vital in giving new technologies the best chance at achieving real-world impact. Here we have attempted to summarise the major components to consider during the development of emerging NGC technologies as a guide for those looking to develop new technology in this domain. We also examine a selection of the latest academic developments from the viewpoint of clinical translation, and discuss areas where we believe further work would be most likely to bring new NGC technologies to the clinic.

Statement of significance

NGCs for peripheral nerve repairs represent an adaptable foundation with potential to incorporate modifications to improve nerve regeneration outcomes. In this review we outline the regulatory processes that functionally distinct NGCs may need to address and explore new modifications and the complications that may need to be addressed during the translation process from bench to clinic.

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1. Introduction

Peripheral nerves function as conduits for signals between the body and the spinal cord (central nervous system, CNS), originating from either the brain stem or spinal cord and travelling to organs where they innervate target tissue and transmit a signal. Compared to the CNS, the peripheral nervous system (PNS) is more susceptible to damage as it lacks protection from the skull and verte-

bral column, and also because it extends to the extremities of the body, which experience greater mechanical and physical stresses. Recovery of patients from peripheral nerve injury (PNI) typically depends on the severity of the injury and the region of nerves involved.

Physical trauma to the PNS can lead to compression and stretching of the nerves and in more serious cases, nerve transection injuries [1]. When these nerves are disrupted, sufferers are left with autonomic, motor, and sensory loss. While the PNS retains some capacity for regeneration, recovery outcomes tend to be poor without surgical intervention, particularly as the size of the gap increases [2–4]. Furthermore, delayed repair has been linked

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to increased risk of poor recovery, particularly with increasing size of the disrupted segment [5]. This often leaves life-long disabilities [6–8]. Injuries due to trauma are predominately in the upper extremities (arms and hands) compared to the lower (feet and legs) [9,10]. Based on the United States of America (USA) medical claim codes and admissions rates for nerve repair and protection the number of repair procedures annually average over 550,000 procedures and projected to increase alongside population growth [11].

Currently, autografts remain the gold standard of treatment for repair of transection injuries, which have the worst treatment outcomes and greatest impact on quality of life. Autografts have significant disadvantages including donor site morbidity, nerve mismatch and additional surgical costs (see Section 2.1.1), and therefore alternative treatments such as nerve guidance conduits (NGCs) and more recently decellularised human allografts have been developed in an attempt to address this. Since their first introduction NGCs, eg. Fastube (K850785; 510k) and Neurotube (K983007), have gone through several iterations to the current standard of device, however they still require significant development to achieve comparable recovery to autografts [12].

Treatments for PNI include surgical procedures, regenerative treatments, pharmaceuticals, neurostimulation and neuromodulation devices, rehabilitative therapies, and more [13–17]. Reviews into these therapies highlight that it is likely that some combination of all the emerging regenerative approaches will lead to an improved peripheral nerve repair after traumatic injury. However, complex regulatory clearance pathways and a present lack of clinical evidence for combination devices and therapeutics currently make them higher risk and therefore set a high barrier to industry adoption. Furthermore, as the healthcare industry is constantly seeking to control costs, for industry adoption, these emerging technologies ideally need to be cost effective or offer superior outcomes that have been demonstrated through clinical trials.

While this review is not a substitute for expert regulatory and development advice, this review aims to explore factors important to development of an NGC technology that is suitable for commercialisation. The review primarily focusses on the pathway for devices released in the USA, as this is often the first major market under a single regulatory body that is targeted by companies developing NGCs. The Food and Drug Administration (FDA) provides an easily accessible, comprehensive database of cleared devices for referral, for example for use in the predicate pathway, and comprehensive guidance documents useful in developing a product through to approval. Whilst more focussed on the FDA, many of the aspects covered in this review are equally applicable to other regulatory agencies and are important areas for de-risking technologies and increasing their likelihood of commercialisation. These factors include an understanding of the biological processes following nerve injury, manufacturing and data required to progress NGCs through regulatory pathways, how they are validated, and potentially modifications to improve repair outcomes for transection nerve injuries.

2. Peripheral nerve structure, composition, and injury

Peripheral nerves are complex tissues that exhibit a hierarchical structure comprised of three distinct layers: an epineurium, perineurium, and endoneurium (Fig. 1) [18–20]. The endoneurium is the innermost layer and surrounds individual nerves and Schwann cells. The perineurium surrounds bundles of nerves to form a fascicular unit acting as a protective barrier for axons (Fig. 1A). The outermost layer is the epineurium, which is a dense layer of connective tissue that surrounds multiple fascicles and microvessels (arterial, venous, and lymphatic), providing additional support to

the multilayer structure. The major components of the extra cellular matrix (ECM) of peripheral nerves consists of protein structures of collagen, laminin, and fibronectin. These proteins form fibrous tubular structures providing support for nerve guidance towards the target tissue (Fig. 1B) [18–20].

PNI covers a range of injuries following traumatic injury which depend on the type (laceration, compression, etc.) and intensity (chronic/acute, minor/major, etc.) of trauma and severity of injury (see Seddon or Sunderland classifications) [6,7,21]. In the most severe PNI, neurotmesis, complete transection of the nerve occurs where both axons and connective tissue separating the nerve into two segments, a proximal portion containing the cell body soma, and distal portion which contains the axon terminal. The larger the transection, the less effectively the nerve repairs itself. Typically, transection requires surgical intervention and addition of materials to enable repair [22,23].

2.1. Peripheral nerve regeneration

Following injury, the separated distal segment begins to degenerate and initiates a cascade of signalling events resulting in Wallerian degeneration, which begins to create a suitable microenvironment for spontaneous regeneration [24,25]. Briefly, this involves the recruitment of macrophages by Schwann cells to clear damaged tissue and myelin sheaths, which prepares the region for regeneration, followed by the degradation of the severed distal stump [26]. Firstly, a fibrin cable forms between the two segments within the first week of repair [27,28]. Schwann cells then begin to proliferate and de-differentiate, into a regenerative phenotype, along the remaining endoneurial tubes, shifting into an elongated morphology and aligning into columns (bands of Büngner) along the existing fibrin cable [29,30]. These regular bands provide physical cues for the regenerating nerve due to the upregulation of adhesion molecules, and secrete neurotrophic chemotactic factors needed for nerve survival and growth, such as nerve growth factor [31]. The nerve will then begin to retrace its previous path from the proximal segment following the path outlaid for it towards the tissue to innervate [31,32]. After the axons begin to sprout, the last phase of recovery is myelination, which is observed around 4 weeks into recovery [27]. Throughout neurogenesis, axons that travel in undesired directions are often pruned however, this is often incomplete and aberrant neurogenesis can lead to the formation of neuromas, bundles of neurite extensions, that can cause life-long pain and discomfort [33]. To achieve full recovery the nerve must undergo all the above processes, Wallerian degeneration, axonal regeneration, and end-organ reinnervation; failure of any of these stages can contribute to impaired functional recovery.

Peripheral nerves regenerate at a rate of approximately 1 mm per day [34]. However, the fibrin cable that spans the transected gap begins to degrade immediately and is fully degraded within roughly 2–4 weeks in humans [28,35]. For this reason, the critical gap size in humans is approximately 30–50 mm; critical gap size is defined as the gap for peripheral nerve regeneration (PNR) which no recovery will be achieved without intervention [36]. Whilst spontaneous recovery is possible the likelihood of successful recovery is reduced with both time and distance. In this case, surgeons will operate and replace the missing segment of nerve with some type of bridging material.

3. Peripheral nerve repair interventions

The standard approach is to attempt to ‘bridge the gap’ either by performing neurorrhaphy, (directly suturing the two ends of the

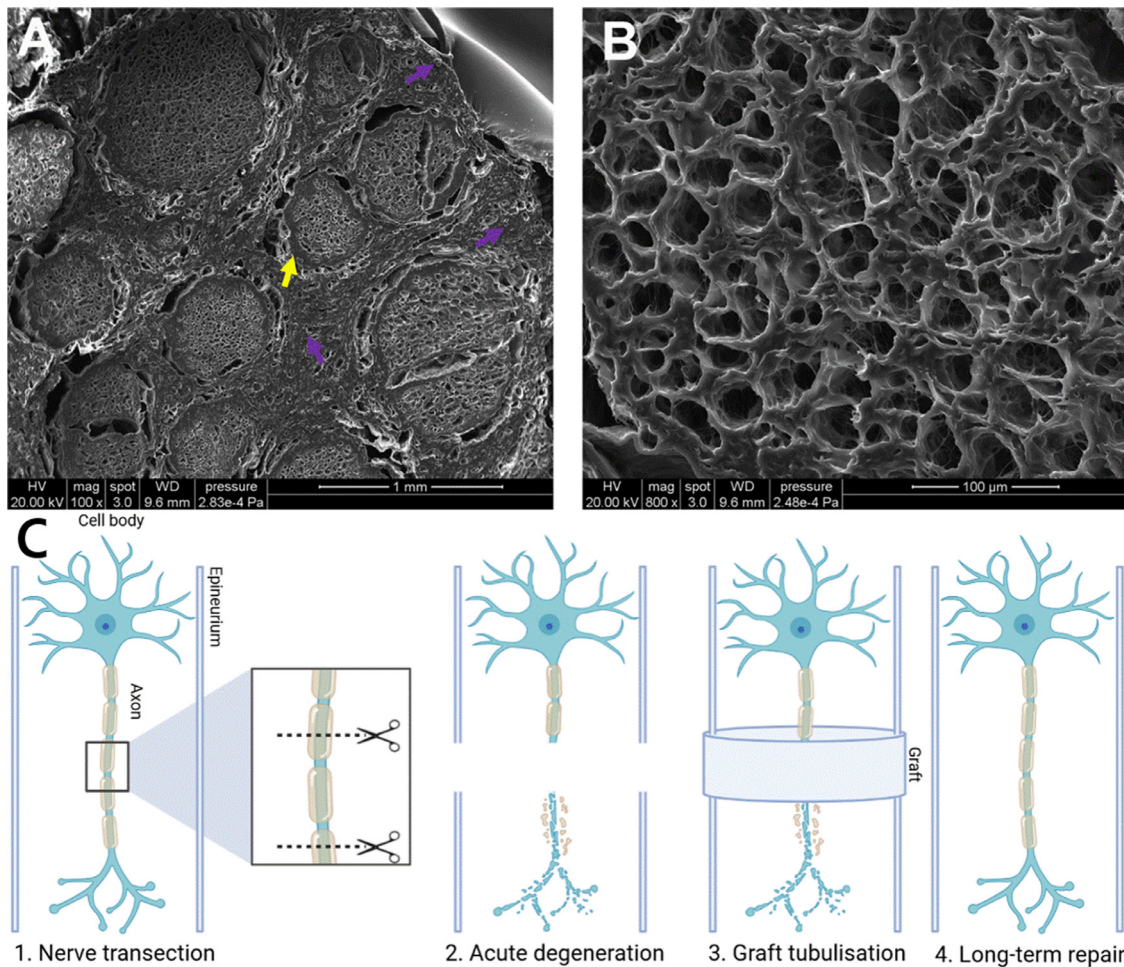


Fig. 1. Structure and repair of peripheral nerves. SEM images of freeze-dried human acellular nerve allograft highlighting the hierarchical structure of peripheral neurons at a magnification of (A) 100X and (B) 1500X. Modified from Zhu et al. [18] Image reproduced under Creative Commons Attribution License. Examples of epineurium (purple) and perineurium (yellow), and fascicles, can be observed in cross sections of the freeze-dried nerve (A). (B) Shows a magnified image of individual endoneurial tubes within a single fascicle. (C) Nerve guidance conduit repair of peripheral nerve transection injuries via graft tubulisation: Following transection injury the distal segment of the nerve undergoes Wallerian degeneration to prepare the injury site for regeneration mechanisms. Surgical repair of the gap via graft tubulisation then assists directional regeneration from the proximal nerve end ideally achieving long-term repair and degradation or remodelling of the graft (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

damaged nerve together) or using a material (autograft, decellularized matrix or otherwise, Fig. 1C) to span the space. To elucidate the most advantageous uses of NGCs, it is important to also understand the advantages and disadvantages of alternative treatments.

Direct suturing is the simplest and cheapest treatment available for peripheral nerve repair but is only applicable where minimal tension will be applied across the nerve [37,38]. This involves approximating the nerve ending margins with sutures and attempting to match the fascicle locations. Generally, suturing is selected as a primary intervention when the transected gap length is less than 10 mm [11]. In some cases, a wrap or NGC will be used as a secondary treatment; generally, in this review we will focus on NGCs that are intended for use as the primary intervention.

In cases where the nerve endings cannot be directly sutured together, alternative solutions are available. The ideal material to repair the damaged segment would be an exact replica of the intact nerve, however due to the complexity of the nerve, patient individuality with size of components and different cell types, and the timelines involved in effective treatment, a human peripheral nerve cannot yet be replicated through tissue engineering efforts. This is where surgeons will often look to use an autograft, allograft, or nerve guidance conduit (NGC) device.

3.1. Nerve transplants

3.1.1. Autograft

Autografts (and allografts, next section) are natural sources of tissue that will have similar properties to the damaged tissue. Autografts are segments of tissue from the patient themselves that are surgically removed from another site and implanted in the injury site to bridge the gap of damaged tissue. These tissues are 'self' and will not undergo a foreign body response. Nerve autografts provide the ideal tissue replacement as they reflect the native tissue chemically, biologically, and structurally. Typically, to treat a PNI, segments of the sural nerve are used [39–41]. Segments of other nerves have also been assessed for similar injuries and in addition to the issues associated with autografts, can also exhibit issues of collapsing, kinking, donor site morbidity, endoneurial and fascicular tube mismatch, and lack of neurotrophic factors [39,42,43]. When repairing a nerve, better regeneration and functional recovery has been observed when a similar nerve type is used to repair the nerve, such as using a donor motor neuron to repair a damaged motor neuron [44,45]. In clinical settings of large gap repair nerve autografts remain the preferred treatment in peripheral nerve repair [11].

Non-neuronal autografts have also been assessed where short segments of blood vessels or blood vessels with muscle tissue (muscle in vein grafts) are used in place of the nerve gap [46–50]. Whilst they are a source of autologous tissue which do not result in sensory/mobility morbidities due to nerve tissue collection, nerve autografts continue to outperform them in nerve repairs. Some clinical studies have reported positive outcomes compared to alternative repair techniques, however there is a lack of pre-clinical and clinical data to support widespread implementation [51,52].

3.1.2. Allograft

Whilst preferred against sacrificing a motor nerve, sacrificing a sensory nerve is clearly not ideal either. Other alternatives have been proposed and investigated such as nerve allografts, which are tissue grafts isolated from cadavers, and theoretically have the advantage of matching the size and neuron type (motor/sensory) specificity to the recipient [53–56]. Nerve allografts contain the endoneurial microstructures required to facilitate nerve regeneration, are a potential source of viable Schwann cells, and have shown comparable recovery to nerve autografts [56]. However, the key major drawback for their implementation is the lifelong prescription of immunosuppressants that predisposes recipients to a number of adverse side effects [56,57].

To reduce allograft immunogenicity, decellularization can be performed to remove cellular components, but due to the removal of Schwann cells, they have been limited to shorter gap lengths so far [54,58,59]. In clinical studies the Avance nerve graft, a decellularized, pre-degenerated, sterilized human nerve allograft, shows favourable regenerative results comparable to FDA cleared NGCs for gap sizes ranging from 5–50 mm [60,61]. Recently, a large multi-centre study examined repair lengths from 3–70 mm using the Avance allograft compared to historical results from autograft or hollow conduits treatment [62]. Safa *et al.* observed meaningful recovery, as assessed by the Mackinnon–Dellon Modification of the Medical Research Council Classification (MRCC) sensory and motor scales [63], in 91% of repairs below 15 mm and 69% of repairs between 50–70 mm, with no reported adverse events. Further improvement of these devices could be achieved by seeding acellular allograft material with autologous Schwann cells (see Section 5.3.3) [53].

Non-neuronal allografts have also been assessed as potential conduit devices in peripheral nerve repair [64–66]. However, these also do not perform as well as a nerve autograft and have limited clinical data to draw from [65].

3.1.3. Xenograft

An alternative to human sourced grafts is to utilize segments of animal nerves through xenografts. The advantage of xenografts is that they have greater availability and reduced cost when compared human allografts, however currently there are no approved non-human nerve tissues for implantation into humans for peripheral nerve repair [67]. Xenogeneic materials have been used widely in NGCs (see Table 1 and Section 5).

3.2. Nerve guidance conduits

Nerve guidance conduits (NGCs) are an alternative to grafted tissue and can be produced from biological materials, synthetic materials, or a combination of both; these are typically formed into a shape of a hollow tube. The first attempt at using a hollow cylinder to repair was reported in 1881, where a hollow bone was used to bridge a gap in a dog model [12]. In the last 40 or so years the hollow NGC models have transitioned from silicone-based materials to more biologically active and compatible materials [12]. Ultimately, these early generation materials

achieved some nerve regeneration in short gap segments, but were non-degradable and required secondary surgery for their removal [68].

NGCs function by retaining diffusion of growth factors and chemoattractants that help direct nerve regeneration through diffusion gradients towards the distal segment, provide protection to the nerve, and impede infiltration of fibrous scar tissue during recovery. NGCs are most commonly used when the transected nerve gap is less than 10 mm, as the hollow conduit NGC design is limited in longer gap repairs where there are poorer outcomes [11,69]. Key features for NGCs have been identified to improve NGC performance [17,35,70]: these include support of axonal regeneration and glial cell proliferation and migration; matching mechanical properties with the encapsulated tissue; being produced from a biodegradable and biocompatible material that allow tissue integration after complete regeneration; and minimising nerve compression during recovery.

3.2.1. FDA-cleared nerve guidance conduits

Currently, there are a range of potential designs for NGC manufacture, however commercially only a select few have received FDA clearance as NGCs [17] (summarised in Table 1). The current FDA-cleared conduits are largely produced from purified bovine collagen, but also include NGCs manufactured from porcine collagen, and xenografts of porcine small intestine. Synthetic polymers that have been cleared for use as components in NGCs include common, well characterized, biomaterial polymers produced from polyglycolic acid, poly(D,L-lactide-co- ϵ -caprolactone), or polyvinyl alcohol.

A current list of approved NGCs can be found under the FDA 510(k) code 'JXI' for nerve cuffs as class II implantable devices [67]. These devices are either intended to be used to bridge a gap, in some cases up to 30 mm, or used as a protective wrap that prevents scar tissue and neuroma formation. A survey of nerve repair surgeons for transected extremity peripheral nerve repair conducted by Brattain found that these devices were used within nerve gap ranges of 5–15 mm [11]. Brattain also determined that as primary interventions of the available treatments, NGCs were utilized 27.7% of the time for gaps below 8.9 mm, 21.1% of the time between 8.9 mm and 20 mm but were not implemented as primary interventions beyond 20 mm. Predominately for large gap repair, surgeons will utilize autografts (78.9%) and processed allografts (21.1%). Kaplan *et al.* also criticized the overwhelming lack of clinical evidence for approaches beyond 50 mm and the need for more complex methods beyond the simplicity of the current FDA-cleared NGCs [71].

A systematic review conducted by Braga Silva *et al.* reported that functional recovery rates for NGCs were above 80% for gaps below 10 mm, but synthetic NGCs had complications that discouraged use [72]. These complications are largely attributable to incomplete reinnervation from axonal dispersion and innervation of diverse target tissue from the same neuron [73].

The key advantages of a NGC over the alternative therapies include the lack of donor site morbidity or requirement for immunosuppressant therapy, with potential for 'off-the-shelf' supply. Their current poor performance can potentially be improved through advancing technology. Promising results from early-stage studies show that NGCs may be capable of inducing regeneration in larger gaps, even beyond 30 mm [74–78]. The NGC designs described in these studies are not without their own challenges and are likely to require significant capital, clinical evaluation, and experimental development before they are suitable for human use.

Table 1

FDA Cleared Nerve Guidance Conduits and Nerve Cuffs under the product code 'JXI'. Modified from the 510(k) FDA database in order of date approved [67].

Product name	Material	510(k) Number	Sterilization Method	Structure	Intended repair length	Company
VersaWrap Nerve Protector	Calcium alginate and hyaluronic acid hydrogel	K201631	Electron Beam	Resorbable, flexible, thin sheet	"no substantial loss of nerve tissue"	Alafair Biosciences, Austin, TX, USA
NeuroShield™	Chitosan	K190246	Ethylene Oxide	Porous, transparent membrane	"no gap" or "gap closure achieved by flexion of the extremity"	Monarch Bioimplants GmbH, Switzerland
Reaxon Plus	Chitosan	K180222 K143711	Ethylene Oxide	Transparent hollow tube	"gap closure achieved by flexion of the extremity"	Medovent GmbH, Mainz, Germany
NeuroFlex™ (Flexible Collagen Nerve Cuff)	Bovine-derived Collagen Type I	K131541	Gamma Irradiation	Flexible, semi-permeable, corrugated, tubular collagen matrix	"gap closure achieved by flexion of the extremity"	Collagen Matrix, Inc., Franklin Lakes, NJ, USA
Reinforced Flexible Collagen Nerve Cuff	Bovine-derived Collagen Type I/unspecified biodegradable polymer	K170656	Ethylene Oxide	Tubular collagen matrix, circumferentially supported with polymer filament	"gap closure achieved by flexion of the extremity"	Collagen Matrix, Inc., Franklin Lakes, NJ, USA
NeuraGen: 3D and 3D Nerve Guide Matrix	Bovine-derived Collagen Type I + porous inner matrix collagen/glycosaminoglycan (chondroitin-6-sulfate)	K163457 K130557	Unspecified	Semipermeable, fibrillar structure of the collagen	"gap closure achieved by flexion of the extremity"	Integra LifeSciences Co, Plainsboro, NJ, USA
AxoGuard™ Nerve Connector	Porcine small intestine	K162741	Ethylene Oxide	Resorbable, permeable wrap	"gap closure achieved by flexion of the extremity"	Cook Biotech Products, West Lafayette, IN, USA
Nerbridge™	Porcine-derived collagen/Polyglycolic acid	K152967	Ethylene Oxide	Resorbable, semipermeable, tubular membrane with porous collagen filler	"no gap" or "gap closure achieved by flexion of the extremity"	Toyoba Co., Ltd. Osaka, Japan
Cova Ortho-nerve Resorbable Collagen Membrane Neurolac™	Porcine-derived Collagen	K103081	Gamma Irradiation	Resorbable, membrane	"no gap" or "gap closure achieved by flexion of the extremity"	Biom'Up Advance Biomaterials, Saint-Priest, France
	Poly(D,L-lactide-co-ε-caprolactone)	K112267 K050573 K032115	Ethylene Oxide	Synthetic and transparent PLCL tubular structure	≤ 20 mm	Polyganics BV, Groningen, Netherlands
Salutunnel™	Polyvinyl alcohol hydrogel	K100382	Gamma Irradiation	Non-biodegradable PVA tubular structure, with a longitudinal slit	"no substantial loss of nerve tissue"	SaluMedica LCC, Atlanta, GA, USA
NeuroMend™ (Collagen Nerve wrap)	Bovine-derived Collagen Type I	K060952	Unspecified	Semipermeable collagen wrap designed to unroll and self-curl	"no substantial loss of nerve tissue" and "gap closure achieved by flexion of the extremity"	Collagen Matrix, Inc., Franklin Lakes, NJ, USA
NeuraWrap™	Bovine-derived Collagen Type I	K041620	Unspecified	Longitudinal slit in the tubular wall structure	"no substantial loss of nerve tissue"	Integra LifeSciences Co, Plainsboro, NJ, USA
NeuroMatrix™ (Collagen Nerve Cuff)	Bovine-derived Collagen Type I	K012814	Gamma Irradiation	Semipermeable tubular collagen matrix	"gap closure achieved by flexion of the extremity"	Collagen Matrix, Inc., Franklin Lakes, NJ, USA
Neurogen Nerve Guide	Collagen (type/species unspecified)	K011168	Unspecified	Porous, absorbable, collagen tube	"gap closure achieved by flexion of the extremity"	Integra LifeSciences Co, Plainsboro, NJ, USA
SaluMedica Nerve Cuff	Polyvinyl alcohol hydrogel	K002098	Electron Beam	Flexible tubular sheath	"no substantial loss of nerve tissue" and "gap closure achieved by flexion of the extremity"	SaluMedica LCC, Atlanta, GA, USA
Neurotube®	Polyglycolic acid, PGA	K983007	Unspecified	Absorbable woven PGA Mesh Tube	≥ 8 mm and ≤ 30 mm	Synovis Micro Companies Alliance, Birmingham, AL, USA
Fastube Nerve Regeneration Device	Not specified	K850785	Unspecified	Unspecified	Not available	Research Medical, Inc., West Midvale, UT, USA
Non-510(k) clearance Avance Nerve Graft	Human decellularized nerve allograft	N/A	Gamma Irradiation	Human decellularized nerve allograft	≤ 70 mm	Axogen Corporation, FL, USA

4. Considerations for the development of advanced nerve guidance conduits

In recent years, there have been a great many publications on new NGC technologies (see Section 5), however these have not yet been translated to the clinic. Many are developed in academic research laboratories that use elaborate technologies and manufacturing processes and combinations of technologies that will require significant further development to be suitable for commercialisation. In order to effectively discuss the development of translatable NGCs in later sections, various portions of the translation pathway for NGCs are discussed in this section.

4.1. Manufacturability

4.1.1. Scale up

New materials, devices, and their manufacturing process should be evaluated based on their ability to be produced on a commercial scale and how easily they can be manufactured [79]. If a multifaceted NGC excels but cannot be reliably scaled up, industry may not further develop the device due to the risks and expertise required to develop new scale manufacturing approaches. The major challenges for scaling up NGC manufacturing techniques typically include production throughput, quality control, stability, purification of biological components, adaptation of complex processes onto a commercial process line, and logistics of product delivery and assembly [79–81]. This requires tight process control and quality control management (ISO 13485) and good manufacturing processes (GMP) at all stages of manufacturing to ensure the quality of product [82].

Looking at the electrospinning technology, there are already a number of commercial electrospun products available on the market used in range of clinical settings such as vascular grafts, fillers for bone voids or as a dural substitute patch [83]. There are many approaches that can be used to scale up manufacturing of the electrospun NGC, one simple method is to increase the number of nozzles and to electrospin over a larger collection area [84]. Scale up of other NGCs can, in some cases, use a similar approach, however this will be entirely dependent on the technique and may require additional process development to permit product scale up.

4.1.2. Sterilization

As part of the manufacturing process of implantable medical devices they are usually terminally sterilized as the final process before being packaged or during the packaging process. Commonly for *in vitro*, and sometimes *in vivo*, experimental procedures in research, implanted materials are sterilized by ultraviolet (UV) radiation or ethanol [85,86]. Whilst it may be acceptable for these applications it is not acceptable for implantation of medical devices into humans. FDA-cleared NGCs are routinely sterilized for implantation by ethylene oxide (EtO) (ISO 11135) or gamma irradiation (ISO 11137). These more aggressive sterilizing environments both have the potential to modify (deleteriously) the properties of some materials [87–91]. It is important that the proposed device is designed in such a way that it can be effectively sterilised as unwarranted modifications due to sterilization can be costly to address late in product development.

FDA-cleared NGCs are primarily terminally sterilized by EtO (Table 1). However, EtO is known to possibly affect material properties after treatment and may not be compatible with some NGCs [88,91]. EtO is classified as a carcinogen and is an environmental concern for residents in the vicinity of sterilization facilities [92]. Furthermore, recent EtO sterilization plant closures and further potential shutdowns may mean that EtO could be an unreliable sterilization method in the future [93]. This has prompted research into alternative established sterilization techniques for

NGCs such as electron beam irradiation, dry heat, and novel techniques such as supercritical carbon dioxide [90,91,94–96]. Recently, the FDA conducted an innovation challenge into alternative sterilization techniques in which supercritical CO₂, nitrogen dioxide, accelerator-based radiation, and vaporized hydrogen peroxide sterilization were assessed [97]. To our knowledge, supercritical CO₂ has not yet been employed in an FDA-cleared NGC device, whereas electron beam sterilisation (employed in the VersaWrap Nerve Protector (Alafair Biosciences)) is from the list of established sterilization methods, approved by the FDA, and has a wealth of literature to draw from. Unlike established methods, novel methods require extensive regulatory testing and collaboration with regulatory bodies to demonstrate equivalence with the established methods. Moving forward, producers of NGCs should be aware of viable alternatives of sterilization should access to their primary sterilization become uncertain.

4.1.3. Design for product integrity

A crucial property of an implantable medical device is its designated shelf life and use-by date. This is the period for which the device can be safely used. Within the FDA-cleared NGCs, shelf life range from 18 months up to 5 years [67]. There are many factors that can impact how readily an implantable medical device can be used 'off the shelf' including: device/material stability, active components (*i.e.* biologicals, eluted drugs, cells, *etc.*), storage conditions, and device reconstitution and assembly (if required, *i.e.* when used as a wrap) [98–100].

The shelf life needs to be sufficient such that product can be made, shipped, and stored such that it still provides ample time to be used in patients. In the current climate of logistics, distribution, and economical access, expedient delivery can be a major challenge to overcome where having a longer shelf life can provide a buffer when these issues are encountered. This is especially important for NGCs that may involve active components in the future as there can be a variety of reasons that timely delivery of the device can be unreliable before or during surgeries [101].

Of the panel of FDA-cleared NGCs, long term storage conditions include dried NGCs in foil pouches, clamshell containers, double blister packages, or double Tyvek pouches [67]. Devices may also need specialised storage conditions such as a low temperature refrigeration or require specific processes to reconstitute them into a functional device before implantation. For example, the Avance Nerve graft is transported, once sealed in a Tyvek pouch, in dry ice and then stored below -40°C for up to 3 years [102]. These specialised storage conditions may be less common in hospitals compared to a specialised research and development facility, can be more difficult to maintain, and may also mean there are specific procedures that need to be followed to permit use. For example, the dry products typically need to be rehydrated before use and this needs to be achieved in a quick and consistent manner such that it does not adversely disrupt the surgical procedures. Likewise, frozen products need to be closely monitored during shipping and storage to ensure they do not thaw, and then need to be thawed completely in a solution before use (such as sterile saline or Lactated Ringers Solution in use of the Avance nerve graft) [102]. Once the devices are reconstituted and thawed, they typically need to be implanted as soon as possible within a certain timeframe. Surgical and logistical delays in this instance may mean the device is unusable and needs to be disposed.

4.2. Regulatory considerations

The regulatory pathway taken by a proposed device will have significant impact on the viability of translating that device. This is generally due to the significant upfront investment needed to prepare regulatory submissions and the risk of unexpected poor

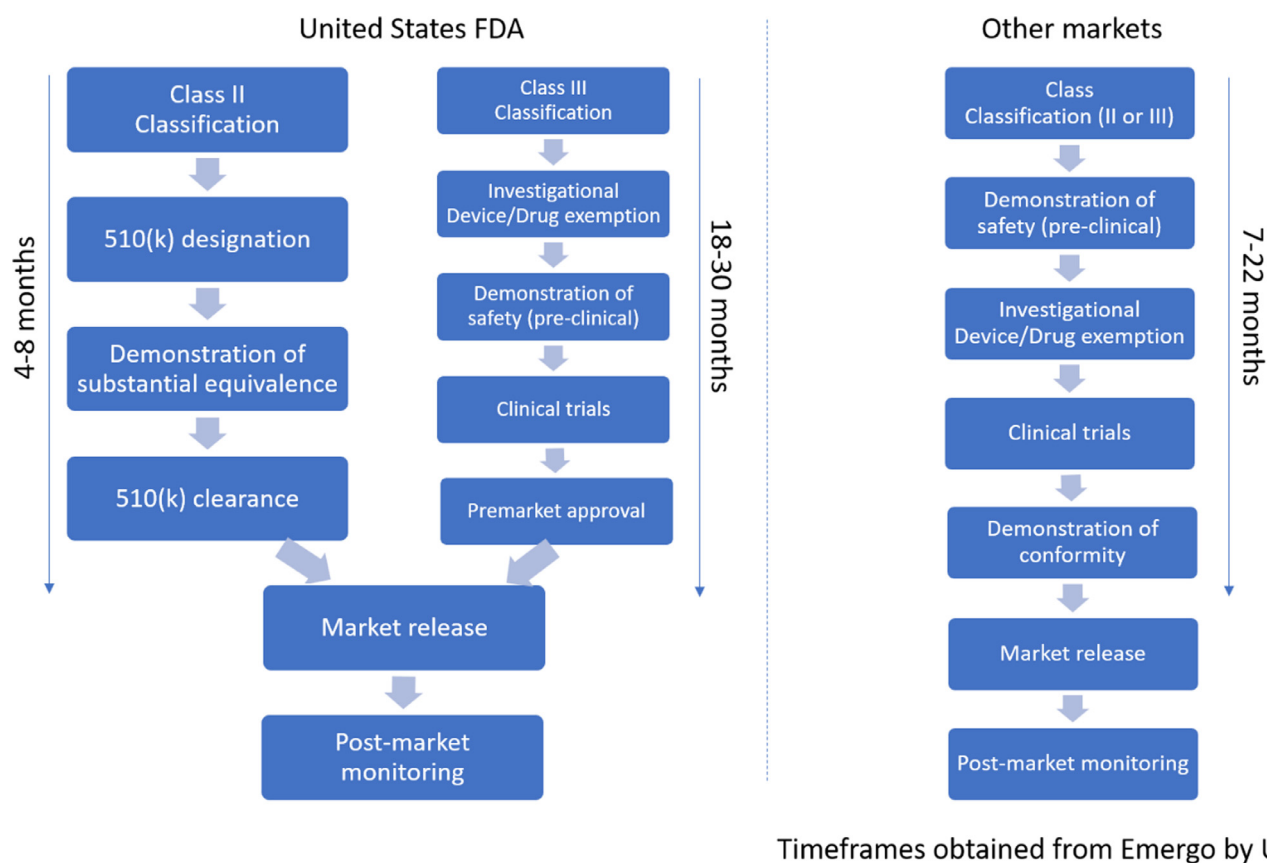


Fig. 2. Regulatory pathways and average timeframe from submission to approval a nerve guidance conduit may take in process towards market approval depending on the country. Timeframe for the submission to approval process obtained from Emergo by UL. [112].

testing results along the development pathway. These must be balanced against the expected gains from producing the device.

A quality management system (QMS) for medical devices is also necessary to ensure these objectives and traceability are met at all stages of device manufacturing and use. An operating and certified system must be in place before a device can be sold, and the QMS should be compliant with 21CFR820 (in the jurisdiction of the FDA) requirements or ISO13485.

4.2.1. Regulatory pathways in major markets

510(k) Pathway (USA)

NGCs have typically been cleared for use in United States by the FDA following an application in the 510(k) pathway (Table 1, Fig. 2) [67]. This requires the manufacturer to provide evidence that demonstrates the new device that they are developing is substantially equivalent to a predicate device. These new devices must demonstrate that they function the same and retain the same intended use as the predicate devices and have a similar level of safety either through *in vitro*, *in vivo*, or clinical data. However, a large proportion of 510(k) cleared devices, as well as NGCs under the 'JXI' product code, do not provide clinical evidence for their devices and rely on a classification of substantial equivalence, with the supporting preclinical efficacy and safety evidence, to be cleared [67,103,104]. Once a 510(k) clearance is obtained, clinical data for the device is then collected to build the clinical safety portfolio for other jurisdictions, where clinical evidence is required for approval. This pathway significantly reduces the risk of developing a new device, by allowing costly clinical testing to take place after the device is effectively on the market and producing revenue.

Minor differences in devices, such that it is not identical to the predicate but rather is substantially equivalent, are possible and have been employed in NGCs seeking clearance via the 510(k) pathway. In this case, it is paramount that the information provided alongside the application proves that the device is safe and effective. Examples of devices that have been approved in this pathway whilst incorporating modifications include the Nerbridge (Toyoba, K152967) and Neuragen (Integra, K163457). Typically, but not necessarily, the predicate devices are from the same field; the Nerbridge NGC incorporates features from Cova Ortho-Nerve (Biom'Up, K103081, a porcine collagen device) and Neurotube (Synovis MCA, K983007, polyglycolic acid (PGA)). For example the Neuragen 510(k) application includes a related non-NGC predicate device, a collagen-glycosaminoglycan bilayer sheet wound dressing [67]. As a further example where material does not need to be identical, Monarch Biomedical's device NeuroShield is a made of chitosan but references predicate devices made of different materials: Cova Ortho-Nerve and Nerbridge (polyglycolic acid and collagen from porcine skin).

The requirement for "substantial equivalence" limits the ability to incorporate new changes in design and materials used, especially if any modifications may alter the intended use of the device. The disadvantage when pursuing a 510(k) pathway with substantial equivalence naturally means there are likely competing products already on the market. This makes introducing a functionally distinct NGC challenging, especially to differentiate the product from the competitors.

Pre-market approval ("de-novo pathway"; USA). In the case where a device does not fulfil the requirements for the 510(k) process, reg-

ulatory approval must be sought via a premarket approval (PMA) through the FDA. This requires preclinical and clinical data (the “*de novo* pathway”), and hence is generally riskier due to high up-front costs; devices that go through this pathway need to promise significant improvements and return on investment to justify this level of risk. As part of this pathway, an investigational device exemption (IDE) can also be submitted, which permits the collection of preliminary clinical data that can later form part of the 510(k) or PMA.

Devices with biological components (USA). Lastly, modifications to NGCs that incorporate the use of biological components (cells, growth factors, drugs, etc.) as part of their therapeutic action will fall under the “combination product” designation. A key consideration impacting the regulatory requirements is mode of action of the product, whether it is a single mode or the action of the two or more combined components. Depending on the mode of action, the FDA will designate a specific agency to regulate via the Office of Combination Products (OCP), either the Centre for Biologicals Evaluation and Research (CBER), Centre for Devices and Radiological Health (CDRH), Centre for Drug Evaluation and Research (CDER) and are subject to 21 CFR part 4 that address the GMP of combination products [105]. The Avance Nerve Graft (AxoGen Corporation) is cleared for use under the 21 CFR Part 1271 Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/P) act and is under the ‘JXI’ product number. To assist in taking a newly developed product to market, if a constituent of the combination product is already FDA approved and/or cleared for this indication, there may already be a safety and efficacy data to draw on (assuming it is available) which may speed the entry into subsequent trials of the combined product. The regulatory pathway the device takes is highly specific to the nature of the combination product. Pre-submission (or Q-sub) feedback can be obtained via the FDA to assist with identifying preclinical performance requirements and the regulatory pathway the device will take [106]. However, constitutive components of these NGCs may require their own preclinical evaluations to demonstrate safety, especially if the combination of multiple parts elicit unintended outcomes. This increase in testing requirements, along with the many uncertainties that stem from the complexity of biological components, again leads to an increase in the threshold at which a product must perform in order to be commercially viable.

Other markets. In Europe medical devices are approved by the European Commission through provision of a European Conformity (CE) mark, but unlike the FDA there is no searchable database of devices. Absorbable NGCs are likely classified as class III implantable devices by the EC and follow a similar approval process to the FDA premarket approval process (Fig. 2), requiring a full design-dossier review including pre-clinical and clinical trial data that comprehensively evaluates the risk of absorbable NGCs under the Medical Device Directive (MDD) 93/42/EEC [107,108]. Australia, Japan, and China require a similar burden of proof before clearance to confirm safety and efficacy, which can create a higher barrier to translation. The international regulations are covered in more detail by Kramer *et al.* and O’Grady and Bordon [109,110]. Comparing the major market regulations, the predicate device pathway offered through the 510(k) of the US FDA is often the first choice for major medical device manufacturers. However, with increasing concern about the predicate device pathway and the need for stringent safety controls in regulatory, rigorous regulatory pathways may become more favourable [111].

4.2.2. Evaluating NGC preclinical safety

In the US, NGCs are generally cleared for market through the FDA 510(k) regulatory pathway by presenting biocompatibility and

functional equivalence to predicate devices using methods from the ISO standards: ISO10993–Biological Evaluation of medical devices, and various other voluntary standards or testing regimes with associated justifications that demonstrate the device’s safety (Table 2) [67]. The summaries of tests used are freely available under the 510(k) summaries or can be accessed via a Freedom of Information (FOI) request. The ISO 10993 guidelines provide a series of methods and guidelines to demonstrate the safety of medical devices. These tests involve a range of biological methods investigating the cytotoxicity, genotoxicity, carcinogenicity, immune responses, and more. NGC safety is further evaluated by assessing the immune response to the implanted material by evaluating the presence of multinucleated giant cells, lymphocytes, activated ED1-immunopositive macrophages, and polymorphonuclear cells [113].

The materials used to manufacture NGCs can introduce varying degrees of risk that can impact the end device’s safety. These considerations should be based on the biocompatibility of the material source, raw ingredients (availability, quality/grade, and reproducibility), chemical exposure during manufacture and sterilization, cost, and whether they degrade or not. Other safety risks associated with material sourcing include: risk of exposure to infectious material (from a type of tissue, animal source, or batch of feedstock), stability of the material in an aggressive environment (used for ensuring material is free of potential pathogens), and batch to batch variation. For NGCs derived from animal products, as each animal is not genotypically or phenotypically identical, within animal derived components there is some variability, which can affect process parameters, and should be accounted for by validating material tolerance specifications to ensure practical batch production is possible enabling a safe and consistent product manufacture [114].

Irrespective of material source, the risks of any additives and processing aids that are incorporated to improve processability should also be characterised and evaluated. For example, collagen-based biomaterials are often isolated from an animal tissue by treating the tissue with a combination of enzymatic digestion and chemical treatments to remove non-collagen components and the remaining collagen crosslinked via crosslinking agents to improve strength, stability, and structure [115]. Likewise, synthetic materials, commonly polyesters, often require solvents to improve viscosity for processability. These chemicals and crosslinking agents used are often toxic and their removal is assessed by measuring residual contaminants.

4.2.3. Evaluating NGC preclinical efficacy: *in vitro* and animal models

Currently, there is no individual standard approach to validate NGCs for peripheral nerve repair; instead, a variety of *in vitro*, *in vivo*, and preclinical tests are performed to demonstrate efficacy. *In vitro* models evaluate the response of various neuronal cell lines (such as PC12, S16, S42, SH-SY5Y, or RSC96), primary Schwann cells or dorsal root ganglions (DRGs), or stem cells that can be differentiated before or after being introduced to the material [116,117]. Morphology assessments of cells typically use pheochromocytoma 12 (PC12) or DRGs to evaluate the alignment and extension of neurites migrating from the cell body. PC12 cells are frequently utilized due to the ease of differentiation into neuron-like cells, although it should be noted that they are not actually neuronal cells [118–120]. When PC12 cells are cultured with nerve growth factor (NGF) they form neuronal-like processes forming sympathetic-neuron-like cells [121]. As these cells originate from a tumour cell line, experiments are often followed up with primary culture and *in vivo* studies to test hypotheses drawn from experiments. Primary peripheral neuronal cultures typically utilise DRGs sourced from rodents and can be prepared from embryonic, postnatal, or adult tissue, and allow the study of neurobiology from different stages of development [73,122–124]. Co-culture models involve combin-

Table 2
Relevant testing standards for nerve guidance conduits.

Biocompatibility	
ISO 10993-1:2018	Biological evaluation of medical devices Part 1: Evaluation and testing within a risk management process
ISO 10993-3:2014	Biological evaluation of medical devices Part 3: Tests for genotoxicity, carcinogenicity and reproductive toxicity
ISO 10993-4:2017	Biological evaluation of medical devices Part 4: Selection of tests for interactions with blood
ISO 10993-5:2009	Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity.
ISO 10993-6:2016	Biological evaluation of medical devices Part 6: Tests for local effects after implantation
ISO 10993-9:2010	Biological evaluation of medical devices Part 9: Framework for identification and quantification of potential degradation products
ISO 10993-10:2013	Biological evaluation of medical devices Part 10: Tests for irritation and skin sensitization
ISO 10993-11:2018	Biological evaluation of medical devices Part 11: Tests for systemic toxicity
ISO 10993-16:2018	Biological evaluation of medical devices Part 16: Toxicokinetic study design for degradation products and leachables
ISO 10993-17:2009	Biological evaluation of medical devices Part 17: Establishment of allowable limits for leachable substances
ISO/TS 10993-20:2006	Biological evaluation of medical devices Part 20: Principles and methods for immunotoxicology testing of medical devices
ISO/TR 10993-22:2017	Biological evaluation of medical devices Part 22: Guidance on nanomaterials
Sterilisation	
ISO 10993-7:2008	Biological evaluation of medical devices Part 7: Ethylene oxide sterilization residuals
EN ISO 11135-2014	Sterilization of health-care products – Ethylene oxide – Requirements for the development, validation and routing control of sterilization process for medical devices
ISO 22442-3	Medical devices utilizing animal tissues and their derivatives – Part 3: Validation of the elimination and/or inactivation of viruses and transmissible spongiform encephalopathy (TSE) agents
ISO 11737-2	Sterilization of health care products – microbiological methods
ISO 11137- 1:2006/AMD 2:2018	Sterilization of health care products – Radiation – Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices – Amendment 2: Revision to 4.3.4 and 11.2
Degradation	
ISO 13781:2017	Implants for surgery – Homopolymers, copolymers and blends on poly(lactide) – In vitro degradation testing
ISO 527-1:2019	Plastics – Determination of tensile properties – Part 1: General principles
ISO 10993-13:2010	Biological evaluation of medical devices Part 13: Identification and quantification of degradation products from polymeric medical devices
ISO 10993-14:2009	Biological evaluation of medical devices Part 14: Identification and quantification of degradation products from ceramics
ISO 10993-15:2009	Biological evaluation of medical devices Part 15: Identification and quantification of degradation products from metals and alloys
Mechanical Properties	
ISO 527-1:2019	Plastics – Determination of tensile properties – Part 1: General principles
ISO 7198:2016	Cardiovascular implants and extracorporeal systems – Vascular prostheses – Tubular vascular grafts and vascular patches
JIS T0401:2013	Mechanical Testing Methods for Stentgrafts
ISO 13934-1:2013	Textiles – Tensile properties of fabrics – Part 1: Determination of maximum force and elongation at maximum force using the strip method
Porosity/permeability	
ISO 845:2006	Cellular plastics and rubbers – Determination of apparent density
JIS Z8807:2012	Methods of measuring density and specific gravity of solid
Miscellaneous	
JIS T 3211:2011	Sterile infusion administration set
ISO 10993-18:2020	Biological evaluation of medical devices Part 18: Chemical characterization of medical device materials within a risk management process
ISO/TS 10993-19:2020	Biological evaluation of medical devices Part 19: Physico-chemical, morphological and topographical characterization of materials
ISO 9001:2015	Quality management systems – Requirements
ISO 13485:2016	Medical devices – Quality management systems – Requirements for regulatory purposes
ISO14971:2019	Medical devices – Application of risk management to medical devices

ing both Schwann cells and neuronal cell types and evaluate the behaviour of Schwann cells migration and neurite extension along topography displayed by the Schwann cells [125,126]. As Schwann cells play an important role in the regeneration processes following traumatic injury (see Sections 2.1.1 and 5.3.3), their behaviour *in vitro* is an early indicator of material performance in peripheral nerve repair.

Compared to the increased risk and scale of tests at later stages, *in vitro* tests are relatively cheap and quick to perform. Due to the range and differences of *in vitro* models available it is important that the tests performed follow the various standards available to allow direct comparisons to be drawn between device iterations.

As the NGC design proceeds through the various stages of development (*in vitro*, *in vivo*, and clinical evaluation), the data generated should provide greater assurance of how the NGC may perform in humans. Currently, the *in vitro* biocompatibility models do not provide sufficient information on the functional performance of NGC in humans, which necessitate the use of *in vivo* testing,

in a number of models, to demonstrate efficacy [116,117]. Unfortunately, this comes with an increasing cost and is often prohibitive to academic researchers. This is a potential area where additional funding (grants, translational studies) or commercial interest can help with continued development, however, the investment risk for companies maybe a deterrent.

Animal models commonly used to demonstrate efficacy in NGCs primarily include rodent and rabbit models; however, other models are also used in the academic and preclinical setting and include mouse, guinea pig, cat, dog, sheep, monkey, and pig [36,67,127]. Whilst the rat and rabbit models can serve to standardise data, their value in predicting clinical utility is uncertain and has been unreliable in NGC translation [71]. The value of large animal models that can more closely resemble human neurobiology to generate more clinically relevant results should be strongly considered [128]. In these animal models, functional performance is demonstrated by successfully supporting the regenerating nerve across the nerve gap compared to autograft repair or predicate devices. In

the rodent models functional recovery is evaluated using grasping and toe spread tests performed over the trial period [129]. Electrophysiological assessment can also be performed on the regenerating nerve by recording the conduction velocity and compound muscle action potential and can be used in larger animal models [117,130]. End point assessments involve histology and immunostaining to assess the morphology of the regenerating nerve and weighing of the innervated muscle [131]. These investigate the g-ratio (the ratio of the inner axonal diameter to the total outer diameter), and density and diameter of axons [132].

4.2.4. Clinical trials

Prior to approaching the clinical trial stage of development, the NGC must have cleared extensive preclinical testing to allow appropriate evaluation of the risk in use of the device. As part of clinical trial requirements in the US, implantable medical devices require an IDE, good clinical practice (GCP) controls in place, and are required to register the trial on a publicly available database (www.clinicaltrials.gov). At this stage of NGC development, the NGC design should be established as any modification needs to be assessed via the earlier standards before human trials.

The Polynerve trial, is a phase I clinical trial (NCT02970864) being conducted in the United Kingdom by the University of Manchester to primarily assess the safety of the device, in a small sample size ($n = 17$) [133]. Polynere is a PCL/PLA co-polymer NGC, with a modified internal lumen surface, and can compare to predicate devices such as Neurolac (Polyganics) and is an indication of improved NGC designs beginning to see clinical translation [133,134]. The secondary aim of the study is to evaluate the efficacy of the device for the repair of gaps between 5–20 mm, which will be assessed by standard sensory outcomes: two-point discrimination test, the Weinstein Enhanced Sensory Test, and Locognosia test.

There are clinical trials currently underway or completed for materials that currently do not have direct predicate devices under the JXI 510(k) pathway such as the Avance human nerve allograft (NCT03964129, NCT00953277, NCT01526681, NCT01809002). In the long-term studies of the Avance nerve graft (RANGER®, NCT01526681), the aim is to enrol a large cohort of participants, from diverse populations (age, sex, nerve location, etc.) and evaluate the performance of the Avance nerve graft over 3 years post-surgery [60,135–137]. The advantage of this broad approach allows identification of sub-populations within the dataset that can be retroactively assessed for outcomes [60]. The Avance allograft is also being tested alongside the addition of bone marrow aspirate concentrate as an adjuvant therapy to improve peripheral nerve repair up to lengths of 70 mm (NCT03964129). In this case, both components of the trial have been assessed individually in earlier trials, however, their combination requires separate evaluation [138]. Should the trial prove successful, other strong candidates in peripheral nerve repair therapies (drugs or growth factors) could also be incorporated in a similar fashion.

4.3. Market size, fit, and utility

A significant component of medical device translation is the de-risking of a medical device as it progresses through its development process up to market clearance and release (Fig. 3). Development of a new medical device requires significant upfront capital and time to facilitate the validation and verification processes necessary to achieve FDA-clearance [139]. For example, the Avance decellularised nerve graft has taken over 20 years from early experiments to the current stage of clinical trials [82]. Likewise, there is a similar delay in translation of modifications to the synthetic NGCs (Polynerve) with almost 10 years of development [134,140,141]. From an investment perspective, there is high risk and an extended period before any return is seen, which provides

a strong motive and justification for manufacturers to follow the 510(k) pathways, where clinical trials may not be required. Planning the process from initial product design, where informed decisions and go/no-go criteria are implemented early through to regulatory approval and market release can be extremely beneficial and can result in significant cost savings along a specific design [142,143].

There are large medical device manufacturers that are already manufacturing and distributing NGCs with appreciable market control and brand identity (see Table 1). To encourage consumers and end-user adoption (hospitals, insurers, patients), the device needs to demonstrate significant benefit, such as reduced cost or increased efficacy, beyond that of currently used devices. While the 510(k) pathway is commonly used to clear NGCs for market release, its requirement for substantial equivalence to a predicate device is likely to make product differentiation more difficult. The alternative is to encourage a paradigm shift through introduction of combination products. Whilst this pathway will be costlier, require significant time, clinical data, investment, and improvement in capabilities compared to current devices, the new device will be in a better position to differentiate itself from others on the market.

5. Manufacturing technologies and designs

Section 4 discusses existing or pre-clinical NGCs and the path to approval and the models they have used to get to the stage of development they have reached (whether cleared or not for final use). A further consideration is whether a design can be manufactured on a scale that makes it commercially viable. There is a wealth of techniques available to NGC manufacturers with the potential to incorporate innovative modifications to the basic hollow conduit design that may have the potential to improve the capacity of peripheral nerves to successfully regenerate across both small and large gaps.

Biologically-derived NGCs are manufactured from ECM proteins such as collagen, gelatin (a collagen derivative), or incorporate coatings such as laminin, that are found in the peripheral nerves, or polysaccharide-based materials such as chitin, chitosan, hyaluronic acid, or cellulose [144–151]. As outlined in Table 1, non-degradable vinyl polymers or degradable polyesters are currently the only synthetic polymers cleared for use. These materials are favoured due to their biocompatibility, ability to support diverse cell types, and biodegradability and have covered in depth by Vijayavenkataraman [152].

NGCs have been manufactured from traditional tissue engineering manufacturing techniques like moulding, freeze-drying, knitting, microbraiding, electrospinning, and dip-coating [86,134,153–159]. Additive manufacturing also offers potential pioneering techniques which include inkjet, extrusion, and lithographic printing methods [76,160–165]. There are many advantages to these new technologies and designs from a prototype and testing perspective, however, caution should be taken through evaluation of scalability and clinical usability of the end product at early stages in their development to confirm design choices as soon as possible.

5.1. Nerve guidance conduit designs

The first generation of NGCs were manufactured from silicone formed into hollow tubes. From there, NGCs were prepared from more biocompatible and biodegradable materials, but still largely retained the hollow conduit design. Emerging NGC designs incorporate highly varied modifications and can be split into three design approaches: filler material, lumen topography, and conduit wall design. These can be combined with a number of techniques to improve nerve regeneration (Fig. 4). In more recent years, newer designs have been cleared for sale, such as the NeurGen 3D Nerve

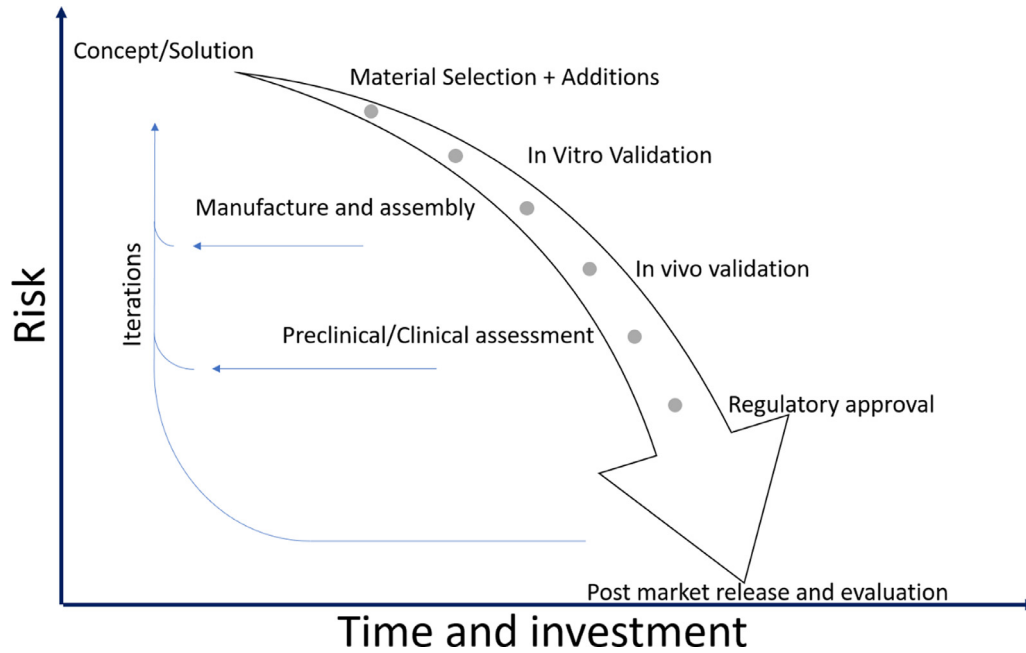


Fig. 3. Iterative development cycle for transition of nerve guidance conduit concept into market available device.

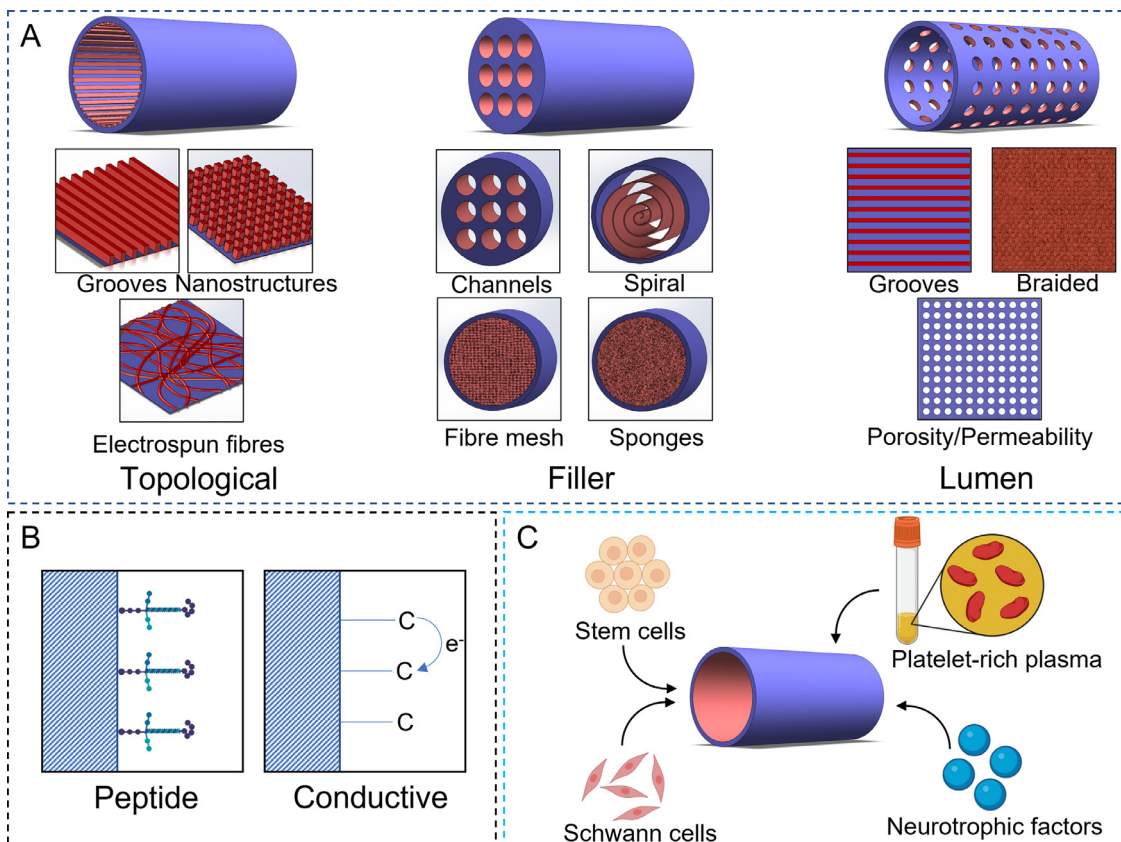


Fig. 4. Approaches to Nerve Conduit Design. (A) Modifications to the hollow nerve guidance conduit are grouped into topological, filler and lumen wall designs are highlighted in red. Modifications include surface patterning (grooves, pillars, surface fibres), filler materials (sponges, fibres, channels), and luminal wall (porosity, permeability, braiding, anisotropic features). These can all be combined with: (B) surface functionalisation (peptides, conductive coatings) to improve attachment and migration of neurons across the surface in addition to (C) biological factors, and neurotrophic factors (such as nerve growth factor) to form the final nerve guidance conduit (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.).

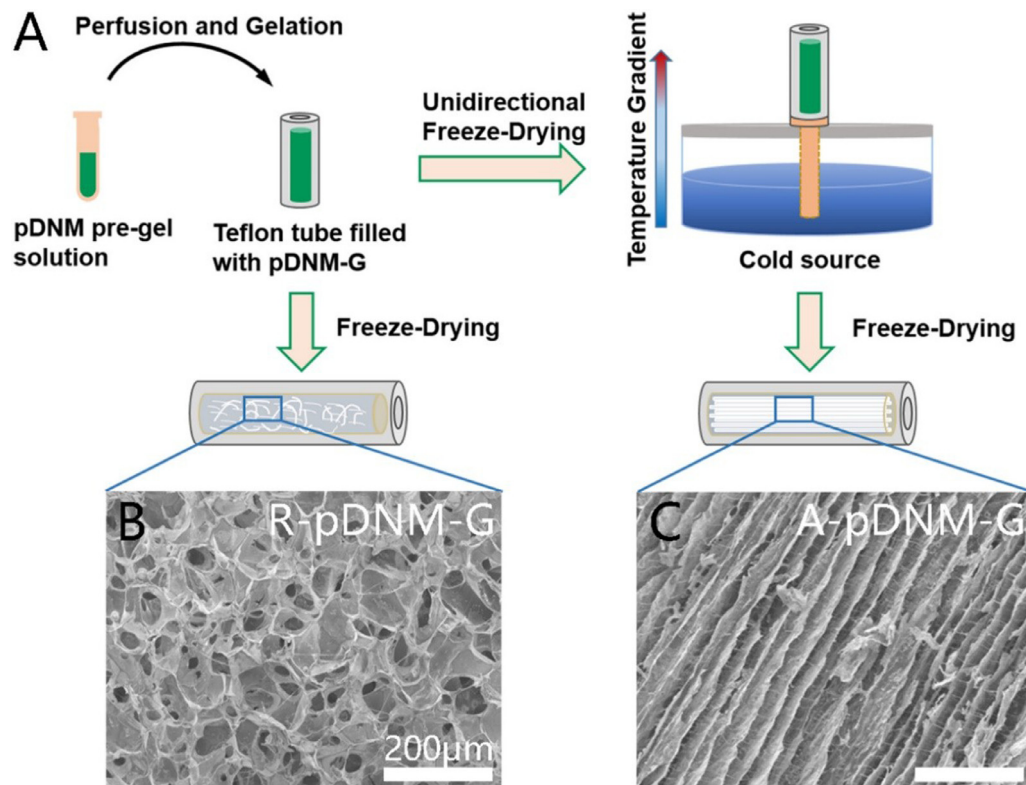


Fig. 5. (A) Schematic illustration of the fabrication process of pDNM-G scaffolds with distinct microstructures. (B) Representative SEM image of cross-sectioned R-pDNM-G scaffold. Scale bar = 200 μm . (C) SEM image of representative longitudinal section in A-pDNM-G scaffold. Scale bars = 200 μm . Reprinted with permissions from Rao et al. [169].

Guide matrix or Nerbridge devices which have internal porous matrices, in comparison to the standard hollow NGC.

5.1.1. NGC lumen filler modifications

The inner lumen space of conventional hollow NGC models can be filled with various materials to enhance peripheral nerve regeneration. Common approaches include utilizing grouped fibres, sponges, aligned channels, or hydrogel fillers of various ECM molecules [94,153,166–169]. Fibre fillings provide similar physical stimuli to topological inner lumen surface modifications due to the inherent topography of the filler material.

Wen and Tresco prepared polypropylene filaments surrounded by a poly(acrylonitrile-co -vinyl chloride) (PAN-PVC) with filament diameters ranging from 30–500 μm [167]. As the diameter of the fibres decreased the migration of Schwann cells and neurite outgrowth was enhanced over a 7-day period from DRG explants. Rao *et al.* prepared a decellularised NGC (Fig. 5) from porcine sciatic nerve and introduced longitudinally aligned microchannels using a unidirectional freeze-drying [169]. Through control of the freeze-drying process, they were able to introduce microchannels ranging from 29–96 μm . When DRG explants were seeded on the inner surface of the microchannels, microchannels with an average channel size of 29–53 μm demonstrated greater neurite extension over 5 days and observed reduced neurite guidance compared to larger microchannels. Interestingly, DRGs cultured on larger microchannels showed a greater tendency to form bundles with greater diameters of nerve fibres over the same timeframe. A similar effect has been observed by Ezra *et al.* where biocompatible fillers, such as collagen-based hydrogels, may potentially impede peripheral nerve regeneration over shorter gaps [170]. They proposed that whilst long gaps may take many weeks to heal, they may benefit from the architecture and Schwann cell support provided by filler

material, whilst shorter gaps may benefit from the native regenerative process that the body undergoes.

As well as the outer tubular structure, the manufacturability of the inner filler materials needs to be considered, as well as the method and consistency of loading for the conduit. This can be challenging in a large-scale production process where high consistency in loading is required. An example of an FDA-cleared NGC that has taken these considerations into design is the NeuraGen 3D Nerve Guide Matrix (Integra). The NeuraGen 3D NGC incorporates a porous inner matrix filler composed of collagen and glycosaminoglycan (chondroitin-6-sulfate) encased in a collagen NGC. Compared to a hollow conduit, the filled NGC demonstrated significant improved bridging and functional motor recovery as observed by increased axon count after 12 weeks of recovery. [166]. Similarly, the Nerbridge product combines both PGA and collagen. PGA is used as the NGC wall to provide strength and protection, whilst a porous collagen hydrogel fills the inner space.

5.1.2. NGC topographical modifications

During PNR axons take on a cone structure during growth in response to topological, chemotactic, and neurotrophic factors. Topographical approaches to improving NGCs look to enhance axonal alignment and minimise axonal dispersion during regeneration by patterning the inner lumen of the material (Fig. 6). These physical features have been shown to improve axonal alignment and directionality when compared to the standard hollow tube design [123,134,171,172]. The parameters that can be varied include the shape, size, spacing, and depth of the features and can impact neurite direction.

Increasing the depth of grooved surfaces is thought to restrict the ability of extending neurites to disperse laterally, perpendicular to the grooved substrate. As the depth of the grooves approaches 8–10 μm neurites preferentially extend along the long

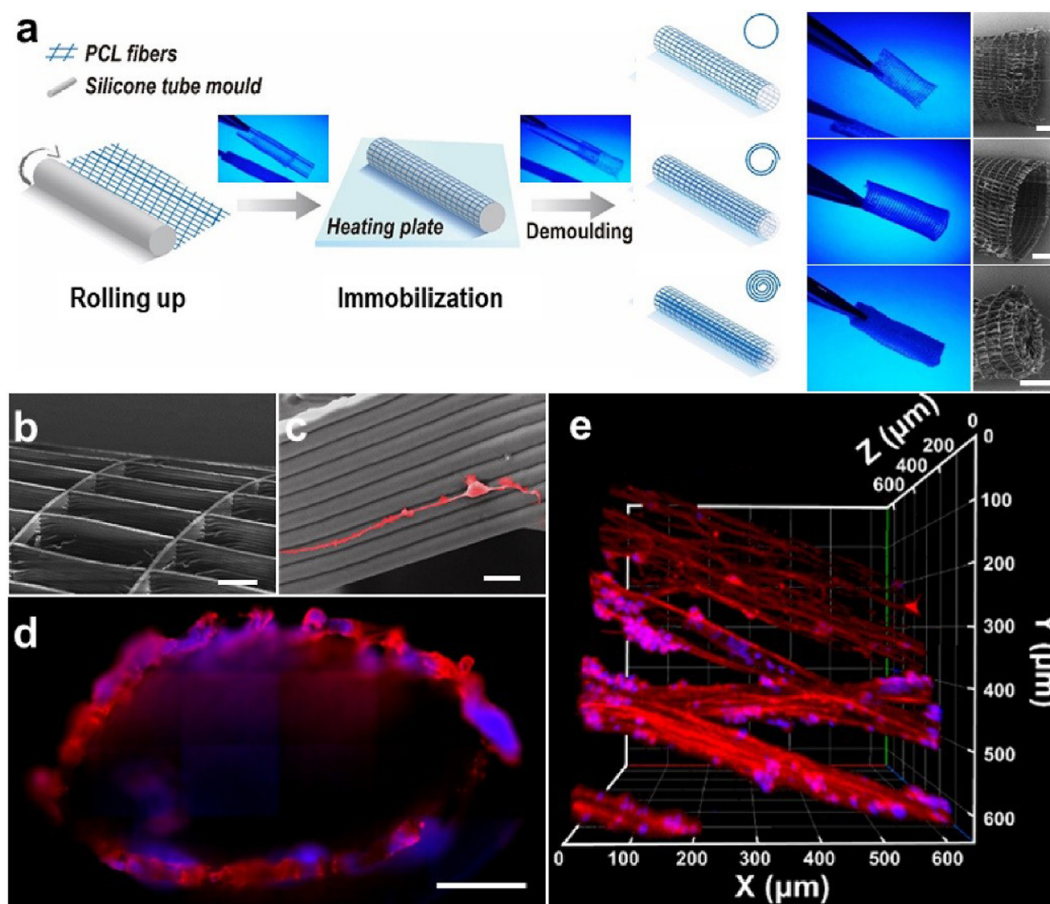


Fig. 6. Template based strategy for the construction of NGCs. (a) Scheme illustration of the template-based construction process. Digital photos of various NGCs were taken under UV lamp irradiation, while SEM images on the right show one head of the conduits. Scale bars: 1 mm. SEM images of (b) a nerve conduit from a rectangular patterned scaffold (1–2) and (c) PC12 cells (pseudocolored red) cultured on the nerve conduit after 14 days of differentiation. Scale bars: 100 μm in (b) and 20 μm in (c). Typical immunofluorescence images of PC12 cells after 14 days differentiation on a nerve conduit including (d) top view on the head, and (e) 3D reconstruction on the luminal surface of the conduit. Cells were stained with TUJ1 (red) and Hoechst (blue). Scale bar: 1 mm in (d). Reprinted with permissions from Zhang et al. [178] (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

axis of the substrate, and is reduced as depth decreases below 100 nm and can be effected by feature type (pillars, grooves, or fibres), and aspect ratio [134,173–178]. Huang *et al.* manufactured patterned poly(ethylene-vinyl acetate) substrates from metallic stampers with dimensions of grooved structures ranging from 396 nm to 1809 nm [177]. Patterned substrates above 905 nm in demonstrated significant neurite alignment and increased neurite extension compared to flat substrates. Grooved structures can be further modified by changing the shape of the groove by forming either V, square, or sloped structures. Of these structures sloped grooves showed significantly improved cell attachment and neurite alignment [140].

Generally, as these features do not modify the device chemistry when comparing to predicate devices, physical modifications to the material structure is unlikely to have significant effect on the regulatory pathway so long as the device as safe as the predicate [179]. This approach is more favourable if it can be easily incorporated into conventional manufacturing techniques. However, care should be taken when structures are on a nanoscale, as these feature sizes may illicit different biological responses compared to the predicate device, and can be hazardous to manufacturers during production (*i.e.* inhalation of particles or fibres) [180]. In these cases, manufacturers may require comprehensive safety evaluation. Whilst these features show a strong effect on the directionality of extending neurites, the feasibility to produce these large features at scale, for example along a 50 mm NGC (human size) compared

to a 10 mm NGC (rodent size), should be considered during manufacture in the later development stages [181].

5.1.3. NGC lumen structure

Besides patterning of the lumen, the bulk material that makes up the NGC wall can be modified to produce non-porous, porous, or semi-permeable NGCs. The FDA-cleared NGCs are either permeable or porous, with the exception of early first-generation conduits that are no longer on the market. Porosity and permeability have been shown to improve the performance of NGCs, especially in synthetic NGCs, allowing vascularisation to occur and permitting fluid exchange between the inner lumen and surroundings in a hollow conduit [156,182–184]. When pore size exceeds 10 μm non-neuronal cells are able to migrate across the lumen wall into the conduit which can obstruct nerve regrowth due to deposited tissue. However, without inter-luminal fluid transfer or if the material swells, a compressive load will be applied within the conduit due to accumulation of extracellular fluid [185]. As such, it is important that manufacturers are able to tightly control the distribution of pore sizes throughout the material during production.

An example of a new design that incorporates all of the physical modifications to the NGC is the spiral bioreactor model (Fig. 7). Here the luminal wall extends into the open space acting as a filler [186–188]. An electrospun layer is added on the surface, which is also used as the sealing material to fix the structure and act as a deterrent to scar tissue infiltration and improve NGC rigidity.

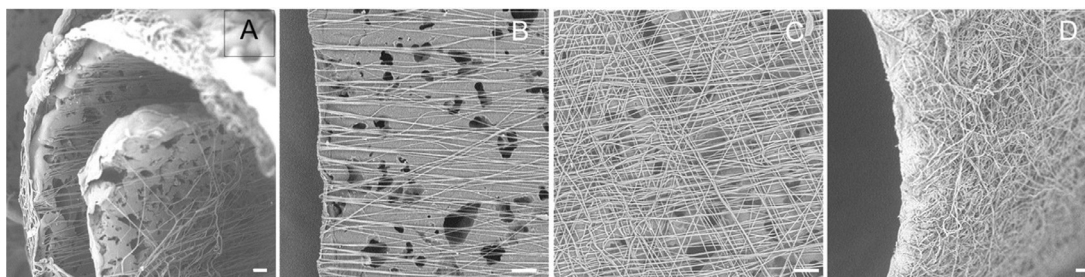


Fig. 7. Scanning electron microscopy images of spiral design PCL Nerve Guidance Conduits. (A) Spiral conduit filler, (B) Aligned lumen wall structure, (C) random nanofiber alignment topography, (D) random outer nanofiber topography. Reprinted from Chang et al. with permissions from Elsevier [186].

Chang *et al.* observed in a 10 mm sciatic nerve defect rodent model an improvement in the compound muscle action potential for the spiral conduit and increased total myelinated axons after 6 weeks implantation compared to a hollow tube [186].

NGCs with modified lumens can be produced via methods such as electrospinning, braiding, porogens templating, and hydrogels [170,189–191]. Fibre manufacturing techniques can produce features with micro- or nano-scaled structures on the inner wall of the NGC and can incorporate porosity alongside topographical structures in the same process [155]. Hydrogels are also common lumen material that can be utilized to form both porous and permeable NGCs and can be produced from both synthetic polymers and various ECM proteins through a variety of manufacturing processes [192–197]. The primary regulatory consideration in lumen selection material chemistry and the biological response to that bulk material. Other challenges depend on the manufacturing method and the complexity involved in production (*i.e.*, casting a bulk cylinder versus assembly of a nanofibrous mesh) which can either be integrated as a single step combining lumen, filler, and topological modifications, or assembled in part. Ultimately, this selection forms the basis of the device and must provide a strong foundation for peripheral nerve repair.

5.2. Surface functionalisation

5.2.1. Peptide and extracellular matrix moieties

It is widely accepted that extracellular matrix molecules improve cell attachment and proliferation for synthetic materials under *in vitro* conditions. Surface coating of NGCs can be a relatively simple process with the potential for improving the efficacy of these material for their intended use and may allow improvements over longer gaps.

Common potential coatings for peripheral nerve repair include proteins such as laminin, collagen I and fibronectin; poly-amino acids such as lysine and ornithine; and peptides such as RGD (Arg-Gly-Asp) or YIGSR (Tyr-Ile-Gly-Ser-Arg). When PCL NGCs are coated with RGD or YIGSR, both Schwann cell attachment and proliferation is improved, and improvement is also seen in DRG explant neurite outgrowth. Under *in vivo* conditions in a rat model, improved vascularization was observed [124]. On a functionalised micropatterned poly(lactic-co-glycolic acid) (PLGA) substrate, greater parallel neurite growth was observed on a laminin coated substrate compared to a collagen I substrate [198]. Klein *et al.* investigated the effects of coating synthetic NGCs in collagen I, laminin, fibronectin, lysine and ornithine. They observed the strongest response from collagen I in conjunction with fibronectin [199]. Similarly, by incorporating VEGF- and BDNF-mimetic peptide epitopes into the hydrogel improved vascularisation, axon density, as well as improved muscle regeneration and electrophysiological behaviour [200]. NGF and BDNF can also be electrostatically bound through functional amine groups to provide a prolonged release of growth factors over a longer period [201].

Glycosaminoglycan (GAG) functionalization has been shown to modulate SC behaviour [202–207]. GAGs comprise a family of linear chains of repeating disaccharide units and provide both structural and functional effects in the ECM. When functionalised onto the surface of synthetic polymers, such as PCL, they have been shown to impact SC behaviour and modify their adhesion, proliferation and differentiation [202]. The further development and utilization of GAGs is promising particularly due to the already FDA-cleared NeuraGen a device, which utilizes chondroitin-6-sulfate is as a material component in a collagen NGC.

These coatings can be expensive to produce, and will cost more than the bulk NGC alone; cost-benefit analysis may limit where they can be applied. This is especially the case because under *in vivo* conditions the material will likely adsorb a range of serum proteins following implantation; this may lessen their positive effects. Furthermore, biological coatings require additional biocompatibility testing due to the chemical changes of the surface, and biologically-derived molecules require source verification and extra quality control during manufacturing to account for variation. Synthetic peptides or recombinant proteins do not have the same problems with batch-to-batch variation, but are typically more expensive to produce.

5.2.2. Conductive coatings

As the function of neurons is to conduct electrical signals, conductive coatings or materials are a popular consideration for nerve regeneration [117,192]. Conductive materials affect the electrical signal transduction on a severed nerve, and are capable of delivering a local electrical stimulus to the regenerating area [208]. Stimulation of neuronal cells on coated material with electric field of 10 mV/cm, which was sufficient depolarization to trigger an action potential, was shown to enhance neurite formation and extension on PLGA nanofibers [209]. Electrical stimulation has also been shown to modulate growth factor production [210,211]. Popular conductive coatings include: polypyrrole, polyaniline, a multiblock copolymer of PLA and a carboxyl-capped aniline pentamer, carbon nanotubes, or graphene oxide-composites [119,192,212–217]. These coatings alongside various electrical stimulation regimes have been shown to improve nerve regeneration. Compared to biological coatings, these coatings can be significantly cheaper due to synthetic commercial processes [218]. These materials and coatings may have poor biocompatibility due to cell adhesion properties, leaching of unreacted components, foreign body response through fibrous capsule formation, and can be difficult to process or incorporate as composite materials due to limited solubility [216,219–221]. This can be minimised by incorporating biocompatible materials or surface treatments, and proper process control and cleaning and may not be significant barriers to translation [219,222]. However, due to change in surface chemistries, further regulatory clearance would also need to be sought despite the underlying material, presumably, being biocompatible.

Table 3
3D printing processes/additive manufacturing utilized in nerve guidance conduit production.

Technique	Process	Advantages	Disadvantages
Extrusion	Mechanical/pneumatic pistons extrude biomaterial in layers along a desired pattern in x-y directions	Large range of materials available Viscous biomaterials can support their own weight Delivery of multiple materials Can be used to deliver cells alongside material at high densities	Lack of mechanical stability of typically extruded biomaterials limit use in NGC formation [231] Maximum resolution of system is limited due to nozzle diameter and material rheological properties Shear during extrusion damages cells (if present)
Stereolithography	Curing of layer in a bath of monomers using a focused laser/light in the x-y directions whilst the build plate translates in the z direction	Smaller feature sizes Does not require heating or extrusion Control over complex geometries: pore size, shape, interconnectivity, porosity	Resolution is limited by system optics Increased print time Limitations with scalability High energy light can damage cells (if present) Limited open source printers and material Equipment cost

5.2.3. Functionalised patterning

Further refinement to these coatings can be added by patterning the coating over the surface or by preparing gradients of peptides or coatings that can promote chemotactic responses during regeneration [173,175,223–225]. Leigh *et al.* patterned laminin perpendicularly to aligned patterned grooves to assess the preference of spiral ganglion neurons to competing patterns to evaluate neurite pathfinding. When the groove depth was increased from 3 μm to 8 μm the effect of either cue was disrupted, whilst at lower groove depths neurites preferred to follow the patterned laminin. This process applies another layer of surface anisotropy to direct regenerating neurites and can be an intuitive approach to improve the synergistic effects of surface topography and chemistry [173]. Patterned coatings will undergo similar regulatory processes as their unpatterned coated counterparts.

5.3. Emerging manufacturing considerations

5.3.1. Conduit manufacturing techniques and additive manufacturing

Additive manufacturing (AM, also known as “3D printing”) covers a range of manufacturing technologies, broadly classified by extrusion and stereolithographic printing (Table 3), which can often produce designs that are impractical to produce using more traditional methods. AM allows customised parts to be manufactured, at the cost of increased production time, with potential to match patient-specific and location-specific features such as bifurcation of a nerve. Predominately, 3D printed NGCs have focused on expanding multi-material and multi-channel NGCs [76,163,226–228].

The FDA and Australia’s Therapeutic Goods Administration (TGA) have recently published guidelines on risk management of additively manufactured medical devices such that the company can demonstrate the ability to consistently meet regulatory requirements (ISO 13485:2016) [229,230]. A particular concern highlighted by Australia’s TGA is the microbiological risk from air bubbles present during manufacturing. These may contain non-sterile surfaces that are difficult to sterilize which could expose a patient to microbes. These techniques provide an option to produce complex geometries out of the same material, but they must also meet the same stringent manufacturing and risk management controls required of their conventionally manufactured counterparts.

5.3.2. Biological factors

Currently there are no FDA-cleared NGCs that use supplemental biological factors alongside NGC implantation for peripheral nerve repair. Folic acid, NGF, BDNF, and polysialic acid, amongst many, have been shown to improve the degree of alignment and quantity of axons [190,232–234]. As indicated by Kornfeld *et al.* they may allow repair beyond 30 mm and can be used to improve re-

covery for shorter segments [235]. Clinical trials for biological factors have been ongoing for decades since their identification [236]. Despite this, their use in commercial products is more complicated due to the lack of controlled release and subsequent diffusion into the surrounding tissue, which can have off-target effects [237]. Many of the issues around biological sourced products (cost, batch-batch variation) also apply to integration of these factors to NGCs. Ideally, for NGCs, their action should enhance the performance of the device without interfering with its mode of action.

5.3.3. Supplementary cells

Several groups have investigated Schwann cells or stem cells to treatments and have observed favourable responses to their presence during recovery [184,238–244]. Cells can be incorporated into an NGC via a variety of approaches for example through homogenous seeding across the NGC surface (Fig. 8) or through carrier support medium (hydrogels, encapsulation, etc.). Schwann cells seeded at high density have been shown to support their own survival through autocrine pathways which inhibits apoptosis and secrete neurotrophic factors that help direct neurogenesis [245–247]. There are limitations of Schwann cell use for repair. It can be difficult to isolate sufficient Schwann cells from adults, primarily due to fibroblast contamination but new isolation processes are being developed to minimise fibroblast growth [248–250]. Alternatively, stem cells may prove viable alternatives to Schwann cells due to their plasticity, immortality, and differentiation potential but also introduce other issues around appropriate regulatory framework [241,251–253].

When using cells (autologous or otherwise) as part of NGC a particular challenge is generating enough for use, which involves a transition from small scale culture systems to industrial processes. This typically requires defined media, in a scalable culture system, under stringent quality control management systems (see ISO 13485) as small changes in the process parameters (pH, O₂, salts, etc.) can generate different cell phenotypes [254,255]. Regional regulatory requirements may influence options and availability when selecting a cell type and source.

Recently, a clinical trial was conducted by Levi *et al.* where they have collected a biopsy for Schwann cells, expanded the cells, transported on ice, and then transplanted to repair a large human nerve defect [250,256,257]. This required an Investigational New Drug approval from the FDA, and Institutional Review Board approval. Before use in surgery, levels of endotoxin were assessed for tolerable amounts (0.7–0.98 EU/kg) and several process controls were employed to remove mitogens, laminin, bovine products, and other process-related contaminants before implantation back into the patient. 15 months post-surgery the patient showed improved proximal sensory and distal motor recovery as well as reduced

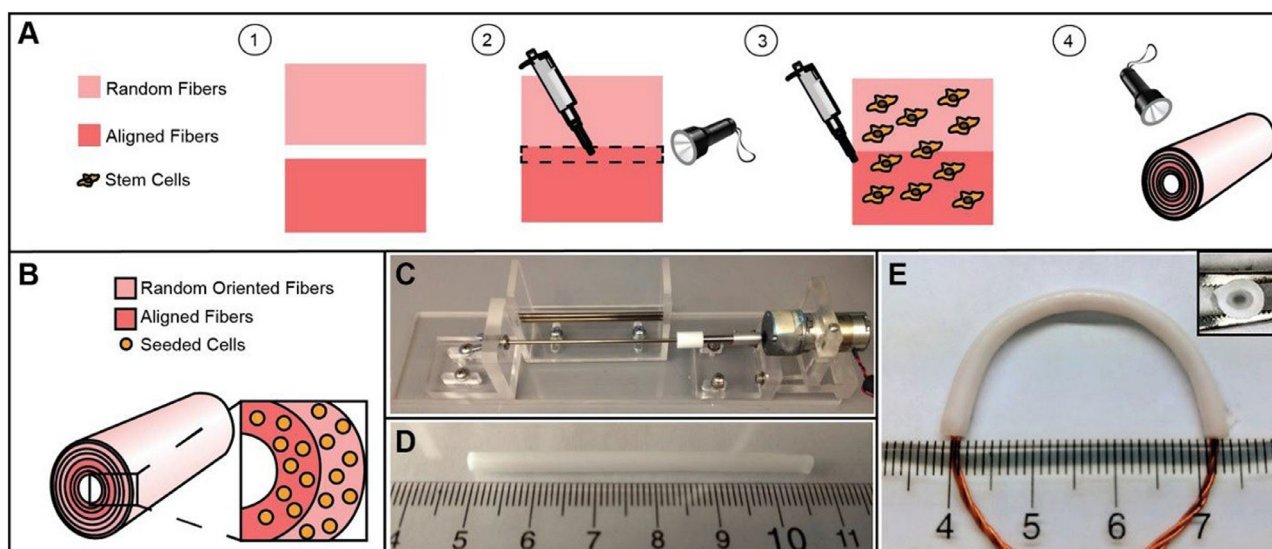


Fig. 8. Construction of nerve conduits with wall-encapsulated cells. (A) Stepwise representation of process. (1) Composite random and aligned PCL/GeIMA scaffolds are (2) overlaid and bonded with photoinitiator solution. (3) The rest of the scaffold is hydrated with photoinitiator solution, and cells are placed on the scaffold (homogeneous seeding is shown here but other seeding approaches are also achievable). (4) The sheet is rolled around a hypodermic needle of desired diameter and cured with visible light to bond layers. (B) Schematic of completed conduit—layers are removed in magnified view for clarity. (C) Prototype machine used to construct scaffold consisting of a slow-rotating motor, a platform, and hypodermic needle. (D) Macroscopic view of 5.5 cm long conduit. (E) Flexibility of conduit at 15.8 mm radius of curvature. Inset: conduit retains patency after full compression. Reprinted with permissions from Sun et al. [251].

pain. Ultimately, the patient received the treatment within 30 days of injury, where collection, isolation, expansion, and purification of the Schwann cells was completed within 14 days [250]. This brief experimental procedure highlights the certainty for sterility and safety from a regulatory perspective. For peripheral nerve repair cells implantation should be viewed as supplementary in conjunction with an NGC or other coaption method as their combined use is currently not FDA-cleared. Currently one active clinical trial is investigating the use of autologous human Schwann cells alongside sural nerve autografts wrapped in a collagen matrix (NCT012510079).

Platelet-rich Plasma:

One alternative supply of autologous factors is to use platelet-rich plasma (PRP) which provides a safe and rich source of growth factors, and has been reviewed in depth by Sánchez et al. [258]. PRP has been studied in combination with NGCs and has also been applied in a number of clinical environments [259–266]. When locally administered in a silicone NGC, PRP was shown to significantly enhance sciatic nerve function and accelerated gastrocnemius muscle regeneration in rats [267]. Recently, Tao *et al.* prepared a hydrogel NGC with live platelets that was capable of supplying sustained release of growth factors [268]. Over a three-month period, the addition of platelets into the NGC showed improved density of myelinated nerve fibres, axon diameter, and CMAP comparable to and autograft repair in a 10 mm rodent sciatic model. As Tao *et al.* have shown, within an NGC, platelets or other factors could be encapsulated within filler material, as part of the lumen, or injected into the periphery around the wound site. Additional considerations such as scaling, route of administration, and half-life should be considered in use of these factors. This will determine the degree of expertise and additional training surgeons will require to assemble the device prior to implantation, or how long the device is stable with active biological factors within the system.

5.4. Combination of multiple modifications

The most clinically effective NGC therapy may involve some combination of cells, neurotrophic factors, and support material

(*i.e.*, a drug-device or biologic-device combination). Combination devices, regulated through the OCP (see Section 4.2.1.), need to demonstrate that their constitutive parts maintain the regulatory benchmark set by current GMP and QMS for each component. These combinations also require design control verification and validation to confirm that there are no negative interactions between constitutive parts and demonstrate that the final product reaches performance targets. However, at this stage the limited clinical evaluation and added regulatory complexity make this challenging to translate and develop at a commercial scale. Furthermore, a consideration must be made whether the NGC manufacturer will implement cell and biological inclusions in-house or licence-in components to avoid infringing third party intellectual property (IP), and may require multiple IP arrangements between several parties. However, the regulatory clearance of the supplement may already be implemented by the third party.

Already there are two cleared combined cell and scaffold (biologic-device) therapies in the US, albeit for indications other than peripheral nerve damage, that are available to use as a framework to develop a combined NGC and cell therapy. Rather than being regulated exclusively by the CDRH through the FDA, these combination products are licensed through the Office of Tissues and Advanced Therapies, under the CBER. GINTUIT (Organogenesis Inc.) combines allogeneic cultured keratinocytes and fibroblasts in bovine collagen for topical treatment of mucogingival conditions. Cells are isolated from donated human newborn foreskin tissue and are multiplied into cell banks. GINTUIT, once assembled, forms a layered structure with an upper and bottom layer containing fibroblasts. This process could be mimicked to form a layered lumen wrap or spiral type NGC [186]. More recently approved, MACI (Vericel Corp.) is a porcine collagen membrane with autologous cultured chondrocytes intended for use in cartilage defect repair in the knee [269]. Cells are collected from a cartilage biopsy and take, on average, 6 weeks before a sufficient population is generated and then implanted alongside the scaffold. These approaches can be quite costly and logistically complex and depending on the level of improvement over existing technologies, may ultimately affect the commercial success of the product.

6. Future directions

Whilst larger gap repair has been the focus of this review, predominantly, NGCs are mostly employed in small gap repair where they have comparable recovery to autografts [11]. There is a wealth of clinical data to draw upon from predicate devices in gap repair of similar lengths which can be used to drive material selection, development, and active component incorporation. Additions of cells, drugs, and anisotropic material designs have strong potential to improve peripheral nerve repair outcomes and reduce the need for autograft use. Currently, most NGCs are approved via the predicate pathway, which requires combination devices to be substantially equivalent to their predicates making it difficult to incorporate additional functionalisation and biologicals. A paradigm shift in the device market is required to change this but will most likely necessitate different regulatory pathways beyond the standard 510(k) FDA approvals and requires greater evidence of safety and efficacy.

As has been noted by several researchers, a particular challenge for material design is the mixture of sensory and motor neurons within a peripheral nerve requiring innervation into specific tissue types to facilitate their function [161]. Johnson *et al.* demonstrated that a regenerating peripheral neuron can be separated into its sensory and motor parts by the differential concentration of the growth factors, NGF and GDNF, to guide bundles of similar neuronal types in a desired direction [161]. This may suggest that there is no 'universal' NGC, as each segment of nerve needs to be 'personalized' for the various arrangements of nerve fibres within to target the original innervation site appropriately, adding more complexity to the design of fully functional NGCs. Furthermore, this leads to the field of personalised medicine, where each NGC is also tailored to the person for size, shape, and nerve conformation.

The potential for recovery beyond 30 mm transections is currently poor; irrespective of treatment approach. Current research highlights approaches that may have potential to push recovery beyond 30 mm [61,74,75,250,257]. Yet these techniques may be underdeveloped commercially, expensive or undesirable for industry to implement, and require clearance through more complex and extensive regulatory pathways.

6.1. Composite and combination design to address large gaps

Clearly, for larger-gap peripheral nerve repair the available NGCs are currently insufficient. Simple ways of improving these devices are to optimise the composition of the mixture of materials, such that it retains the favourable features of all components [154,160,164,211,270]. For example, biologically derived materials typically display better biocompatibility compared to synthetic materials, which can instead provide higher stiffness and greater protection to the structure. Similarly, by combining multiple design approaches, such as filler and wall modifications alongside cell seeding and other biological factors, improvements in PNR outcomes are obtained using common polyester based biomaterials [77,141,271,272]. However, the regulatory timeframes for these additions can be significantly longer than the pre-market approval process for a standalone device, especially if the addition is not cleared for use under the same indication [112,273,274].

A major challenge for combination designs is the lack of appropriate predicate devices to support a 510(k) application. The greater levels of investment that are required for a pre-market approval, coupled with the greater complexity of the production and quality control processes, mean that such a device is significantly harder to justify. It is therefore vital that early research is standardised to allow these larger investments to proceed with high confidence.

7. Conclusions

Peripheral NGCs have seen significant development and change since the first iteration of the device. However, there has been a delay in translation of innovative design concepts into clinical trial and post market phases. Recent advances in NGC design and combination with multiple active constituents will necessitate regulatory approval other than the predicate device pathway if they are to move into clinical use. To further accelerate emerging NGC translation, there is a need for standardisation of testing that can be used to validate and assist verification of key requirements that will serve to de-risk the device at earlier stages of development.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Dr David Rhodes is a founder and Chief Scientific Officer of ReNerve Pty Ltd.

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