Section VII

Computers, Engineering, and the Future

Table 38.1 The Five Major Phases and Decision Gates for Medical Device Development

This process is applicable to a broad range of medical technologies and may be used to develop sophisticated premarket approval and premarket notification (510[k]) devices and less sophisticated devices that may be exempt from most regulatory requirements.

- Phase I/gate 1: Initiation, opportunity, and risk analysis
- Phase II/gate 2: Formulation, concept, and feasibility
- Phase III/gate 3: Design, development, verification, and validation
- Phase IV/gate 4: Final validation and product launch preparation
- Phase V: Product launch and post-launch assessment

From Pietzsch JB, Shluzas LA, Pate-Cornell ME, et al. Stage-gate process for the development of medical devices. J Med Dev 2009;3:021004–15.

maximize the value of the information obtained from potential customers, a structured approach, such as quality functional deployment (QFD)[11] is recommended. The reason that this process is so powerful is that it is a well-defined process to translate customer needs to product features and keep them evident throughout the design process.

The final step in this phase of the design process is to thoroughly document the product requirements.[12] Though there is some disagreement, requirements should state only what the product should do and not how it does it. This approach provides the broadest palette for conceptual designs.

Conceptual Design

Conceptual design is the process of structuring a solution to a design problem. During this stage the process is mostly qualitative, not quantitative. For instance, if one were designing a robotic surgical assistant, a choice between electric and hydraulic actuators would be decided during this phase. This decision may require some quantitative analysis. For example, "Can a motor fit within the space allotted and still provide sufficient motive force without requiring the user to specify part numbers, bolt patterns, and so on."[13]

For engineers, the conceptual design phase is usually the most enjoyable. Conceptual design requires great creativity, as a number of widely disparate approaches should be developed to ensure that the best ones are considered for further development. Methods used to generate ideas include (1) literature searches, (2) biomimicry, (3) reverse engineering of related products, (4) study of analogous systems, and (5) brainstorming, among others. Once a number of concepts have been developed, they are assessed against the requirements previously developed to determine those that best meet the specified needs.

At this juncture it is important to note several issues that are relevant to design of medical devices rather than other product types. In the United States, the Food and Drug Administration (FDA) regulates medical devices. Although entire books are written on the subject of complying with FDA requirements,[14-16] the following two (and potentially three) issues greatly affect the development process.[17]

Record Keeping

The Safe Medical Devices Act of 1990 added design validation requirements to the Good Manufacturing Practices (GMP) requirements.[18] Fundamentally, the entity that designs a medical device must document the procedures used to ensure that the specified requirements are met. Procedures should be generic rather than detailed. That is, they should include major activities and assignments for subsystems, as opposed to detailing responsibility for component selection. It also is understood that design procedures change, thus the standard requires that an entity's procedure be regularly reviewed and updated.

Device Class

All medical devices are categorized into one of three device classes:

- Class I: These are non–life-sustaining devices whose failure poses no risk to life. Examples of class I devices include bandages, stethoscopes, and examination gloves. Most class I devices are exempt from the premarket notification or GMP regulation.
- Class II: These devices are non–life sustaining; however, the controls in place for class I devices are insufficient to ensure safety and effectiveness. Examples of class II devices include catheters, powered wheelchairs, and many clinical chemistry test systems. Although some class II devices are exempt from premarket notification, others may require clinical studies as rigorous as an investigational device exemption (IDE) for premarket approval (PMA).
- Class III: These devices are typically those that support or sustain human life and whose failure is life threatening. Examples of class III devices include heart valves, implanted electrical devices, and joint implants. The vast majority of class III devices require PMA, a process that includes laboratory testing, animal testing, failure mode analysis, manufacturing standards, and safety and efficacy testing as determined in a human clinical trial. Needless to say, to obtain PMA can be a long, costly process.

When setting out to develop a medical device, the design team should determine the device class, as early as possible so that the planning process can incorporate the appropriate activities into the overall project plan. For new devices for which precedent is unclear, the design team should submit a Request for Determination to the FDA.

Extent of Business Activities

In the grossest sense, the activities needed to bring a device to market are conception, design, production, distribution, and support. A key decision for a new business entity is to determine which of these activities are to be performed in-house and which are outsourced. This decision has two major impacts: first, the amount of investment needed, and second, the FDA regulations that must be addressed. For many companies, outsourcing manufacturing offers a good blend of activities, allowing the company to minimize capital costs, earn a reasonable rate of return, and reduce FDA regulatory issues (though the manufacturing partner must comply with FDA requirements).

The conceptual design phase ends with a design review that presents the requirements, the concepts developed, and the concept(s) selected for further development.

Detail Design

Most novel designs includes one, and sometimes more, elements that have not been previously realized. For example, lab-on-chip devices replace manual fluid introduction and mixing with microfluidic components. Before the design for the final product is completed, the development team typically performs a series of experiments to validate the functionality of the novel component.[8] Staying with the example, do the microfluidic devices deliver sufficient head and flow to provide sufficient agitation?

Once all of the subsystems are known to work, it is common to couple all of them together in a bench-top prototype to assess overall system functionality. This prototype may bear little physical resemblance to the final device. However, the manner in which it operates is analogous. Depending on the nature of the product, the bench-top prototype may be used to perform in vitro or in vivo testing, again providing further evidence of the device's safety and efficacy.

Once this testing is completed, the team should have sufficient information to design the final device. This detailed design consists of all of the information necessary to reliably and repeatedly produce the device. Often, methods such as Design for Six Sigma[19,20] are used to help ensure that changes in performance due to manufacturing variations do not result in performance falling outside the specified bounds. This design phase ends with a review that presents the results of the experiments performed, the detail design, the bill of materials, and how these perform together to meet the design specifications.

Clinical Trials

Certain classes of medical device must undergo clinical investigation[21] before the FDA provides marketing approval. Animal model testing often is performed before human trials, especially in those cases for which safety and efficacy are unknown. Animal use to test a device is a privilege and numerous controls exist to ensure that no more than the minimum number of animals are used, that they are properly housed and cared for, and that upon the conclusion of the experiment, they are humanely euthanized.

The institutional review board of the facility that oversees the trial must approve all devices that undergo human clinical investigation. In addition, the FDA must approve trials for significant risk devices through submission of an IDE. The IDE exempts the manufacturer from certain portions of the Food, Drug, and Cosmetic (FD&C) Act during the trial phase. However, the manufacturer is still required to comply with all design controls and all necessary manufacturing controls to ensure patient safety and compliance with the manufacturer's quality claims.

The goal of a clinical trial is to determine the safety of a device and its effectiveness in terms of the intended claims.[22] This requires concise and specific definition of the study's objectives. The objectives must consider factors such as comparison to approved modalities of treatment or whether it treats a symptom or an underlying cause. Once these factors are known, details of the trail design, such as study size, candidate pool, and controls, among others can be formulated. In addition, trials must be carefully designed to minimize errors and biases. From a business perspective, trial design is critical because the claims that the business wishes to make about its device must be supported by clinical outcomes.

Manufacturing

Once the design is completed, a pilot run is performed to validate manufacturing processes. This is the first build of the device in its final form using the manufacturing documentation. This part of the process also includes assembly workforce training, validation of supplier plans, and checking that manufacturing objectives have been achieved.[23]

A critical aspect of this phase is product packaging and labeling. Packaging must be designed to ensure that the product reaches the end-user in an appropriate condition (which typically means that the product maintains sterility) and that the package can be easily opened. Labeling includes all printed or graphic material that accompanies a product and advertising. Depending on the type of product, labeling requirements may include the manufacturer's contact information, intended uses, and directions for use, to name a few.

Once all of this information is available, it is submitted to the FDA, either as a 510(k) premarket notification submission or a PMA submission. Approval from the FDA is required to legally offer the product for sale in the United States. Other regulations apply in other countries. However, FDA approval is not necessarily sufficient for the product to gain acceptance. In the United States, much of the cost for medical products and procedures is paid for by third-party insurers. Underlying these payments is a list of codes that source from the Centers for Medicare & Medicaid Services (CMS). Because codes are defined in terms of services provided, and not specific devices, new products may be covered by existing codes. However, novel devices may require the development of new CMS codes, and without these codes, many practitioners may be hesitant to adopt a new device.

Financing Product Development

A corollary to Murphy's law states, "The first 90% of the task takes 90% of the money, and the last 10% takes the other 90%." Based on the previous discussion about medical device design and development, this statement may, in fact, be overly optimistic. Depending on the type of device, the development process can require years and tens of millions of dollars. Because most medical device inventors are not independently wealthy, outside investment often is required to bring a new medical device to market.

The world of outside investment can be broadly divided into two categories: those who invest primarily to obtain a (hopefully very high) return on their investment and all others. The former are typified by angel investors and venture capitalists; the latter by universities, federal and state governments, family, and others. Angel investors and venture capitalists play such an important role in medical device development that the entire next section is devoted to them. This section starts with some general guidance about business practices and then discusses non-equity investment opportunities.

The founder of a business focused on developing a new medical device is convinced of the value and importance of the invention. However, Ralph Waldo Emerson's adage that if one "build[s] a better mousetrap and the world will beat a path to your door" is not always true. It takes considerable effort to convince others that the potential product will both address an important medical need and produce a profit.[24] Simply providing experimental data is insufficient because the inventor will be asking potential investors to trust him or her with millions of dollars.

To access outside funding of most any sort, a company must have a business plan.[25,26] There are innumerable books about writing business plans[27,28] (see further suggestions later in this chapter). Two cautionary notes: first, most business plan software programs should be avoided, because they typically do not add much value. Second, the writing of the plan should not be outsourced because the entrepreneur must know the entire plan, the sources used to develop it, and so on. Contained within the plan is a financial model,[29] arguably the single most important aspect of the plan. Attention should be focused on building a rational model, because potential investors will be more interested in the assumptions that underlie the model rather than the actual number presented.

As a final cautionary note, inventors who intend to seek outside investment should engage accountants and attorneys. Although it is true that forming a business requires little more than completing a simple form, the business's rules of operation (referred to as an operating agreement for limited liability companies [LLCs] and bylaws for corporations) dictate how the business is run. If these rules of operation are not professionally written, they may impede potential investments. Similarly, an accounting system that does not adhere to generally accepted accounting principles (GAAPs) will make it very difficult for a proper financial analysis to be performed, which again may impede potential investments. As a technology-focused business, the most valuable assets are the inventor's intellectual property. Although it is certainly possible to apply for patents and trademarks independently, engaging an intellectual property (IP) attorney is strongly recommended to ensure that the protection sought is as broad as possible. Finally, an attorney should review all dealings that can materially affect the business, such as grants of corporate ownership, licensing agreements, and partnering deals, among others, before being executed.

University Research

If the developer is a university employee when the medical device idea is first invented, the first stop is the school's office of technology transfer. Since the passage of the University and Small Business Patent Procedures Act (also known as the Bayh-Dole Act) in 1980, most universities have created offices that deal exclusively with licensing and IP. For a university inventor, working with the office of technology transfer provides several important benefits. First, as dictated by the Bayh-Dole Act, if the research was funded by the federal government, the university has the right to retain ownership of the IP created. As such, should the technology be commercialized, the inventor will typically receive financial remuneration as a percentage of the licensing revenue earned by the university. Second, the inventor of the IP is often granted first right-of-refusal with regard to licensing the technology for commercial purposes. Often, for faculty-founded start-ups, the university will provide favorable terms, such as defraying patent prosecution costs until the company has revenue. Third, the office of technology transfer may have specialists whose role is to help with company formation. These individuals can provide guidance with business plan writing, recommendations for local service providers, and identification of funding opportunities.

The passage of the Bayh-Dole Act also has motivated universities to commercialize technology. Universities with active technology transfer offices can generate tens of millions of dollars annually in license fees, royalty, and equity. To capitalize on this opportunity, a number of states and universities have created funding sources for university inventors to assist them to bring their inventions to market. Examples of such programs include the following:

- Boston University Ignition Award and Launch Award[30]: The former helps bridge the gap between basic science and the product development and the latter is designed to help faculty members start new companies based on technologies that they invented at the university.
- Michigan Universities Commercialization Initiative[31]: A collaboration designed to complement and enhance the technology transfer at Michigan academic and research institutions by supporting commercialization of IP.
- University of Utah Technology Commercialization Project[32]: Focused on further developing novel technologies that are near commercialization in all areas of technology.

For the university inventor, such initiatives offer great value. First, the competition for funds is limited to a small pool of applicants, thus the odds of funding are relatively high. Second, the peer-review process typically used provides some validation of the commercial potential of the technology. Third, the funds often can be used for non–technology-focused activities, such as engaging business and marketing professionals from outside the university, which helps to accelerate the growth of the business. The only downside to these programs is that the funding available is typically limited.

Government Research Funds

Growing a technology-focused start-up from inception to profitability is a very high-risk proposition. Though exact figures are not available, it is estimated that less than one quarter of all businesses are still operational after 10 years—for technology-focused start-ups, the number is smaller. On the other hand, new products and companies account for a disproportionate fraction of a country's gross domestic product (GDP).[33] As such, all levels of government are incentivized to support early-stage companies because of the potential return on investment. In the United States, one federally mandated program that supports small businesses dominates all others: the Small Business Innovation Research (SBIR) program (and the very closely related Small Business Technology Transfer [STTR] program).[34,35]

Originally authorized by Congress in 1982, key objectives of the programs are to stimulate U.S. technologic innovation, create new opportunities for small businesses to participate in federally sponsored research and development, and increase private-sector commercialization of innovations derived from federal research and development (R&D). As legislated, all

	SBIR	STTR
Phase I Feasibility	6 months $100k	12 months $100k
Phase II Prototype	2 years $750k	2 years $750k
Phase III Commercialization	As long as it takes non-SBIR/STTR funding	

Fig. 38.1 General time and funding outline for Small Business Innovation Research (SBIR) and Small Business Technology Transfer (STTR) programs.

federal agencies whose extramural research and development budgets exceed $100 million have a mandated set-aside of 2.5% of their budget to fund SBIR projects. In addition, all federal agencies whose extramural research and development budgets exceed $1 billion have a mandated set aside of 0.3% of their budget to fund STTR projects. In fiscal year (FY) 2007, 12 agencies participated in the SBIR/STTR program, with total funding of $2.315 billion.

Of the 12 participating agencies, the Department of Defense (DOD) accounted for 54.9%, the National Institutes of Health (NIH) accounted for 28.1%, and the National Aeronautics and Space Administration (NASA), Department of Energy (DOE), and National Science Foundation (NSF) combined accounted for 14.2% of the of the total funding, respectively. Developers of medical devices would typically focus on applications to the NIH; however, the DOD and NSF occasionally seek medical device applications as well.

SBIR/STTR programs are three-phased programs, as outlined in **Figure 38.1**. The durations and dollar figures are statutory guidelines—each agency sets its own rules.

The key requirements to allow access to the source of funding are that the firm be a U.S. for-profit business with 500 or fewer employees and that work be performed in the United States. Other requirements about corporate ownership, principal investigator employment, and so on can be found online. Major changes to the SBIR program are being proposed in Congress during the production of this book, and so the information provided herein is likely to change. (The reader may refer to information about these programs online at www.sbir.gov.)

Participating in the program is straightforward. A small business must first obtain a data universal numbering system (DUNS) number (fedgov.dnb.com), federal tax identification number (www.irs.gov), and a bank account that accepts electronic funds transfers, and then register with the central contractor registration (www.ccr.gov). Next, the small business reads the solicitations published by the 12 agencies and applies for phase I projects for which it is qualified. The phase I application takes the form of a proposal along with a project budget, brief resumes of key personnel, and letters of support from partners or customers. Small businesses that successfully complete a phase I project will almost always be invited to submit a phase II proposal. The phase II proposal is very much like the phase I, but with two additions: a section that describes the outcome of the phase I project, and a commercialization plan that describes how the technology being developed will be brought to market.

There are some important differences between the SBIR/STTR programs offered by the agencies. The DOD and several others are contracting agencies, whereas the NIH and NSF and others are granting agencies. With contracting agencies the agency establishes the needs (which are typically highly focused), there are more fiscal requirements, and the project initiator (who works for the agency) is the primary proposal reviewer. With granting agencies, the investigator identifies the problem and specifies the approach (as long as it falls within the agency's purview), there is more fiscal flexibility, and proposals are peer reviewed. From a business perspective, winning SBIR contracts from contracting agencies is beneficial because on successful completion of phase II, the agency may wish to purchase the product that has just been developed. Winning SBIR contracts from granting agencies is beneficial because this indicates that the technology was deemed meritorious to a panel of experts, and so provides great credibility to the company.

As valuable as the SBIR/STTR programs are, all potential applicants for SBIR/STTR funding should be aware of several facts:

- The programs are highly competitive. On average, fewer than one in eight phase I proposals is funded and typically half of all phase II proposals are funded.
- Federal funding has restrictions. Project money may not be used for certain necessary business activities such as patent prosecution, thus other sources of financing are required.
- The SBIR/STTR cycle is slow. It is not atypical for a project (defined as the first writing of a phase I proposal to the end of the phase II project) to exceed 3.5 years. For certain types of products, where time-to-market is important, this long time frame may not be acceptable.
- The federal government has rights to IP developed. Quoting a recent DOD SBIR solicitation: "The government receives a royalty-free license for its use, reserves the right to require the patent holder to license others in certain limited circumstances, and requires that anyone exclusively licensed to sell the invention in the United States must normally manufacture it domestically."

State Commercialization Funds

State governments realize that having a vibrant start-up community is valuable for the state. Companies that become successful will hire more people, spend more money, and pay more taxes. To help build such communities, many states have created programs that support technology-focused start-up businesses. Such programs span the gamut from business plan competitions that provide ten of thousands of dollars to SBIR matching programs that offer hundreds of thousands of dollars to other competitive programs that provide millions of dollars. The following list highlights several such programs.

- Texas Emerging Technology Fund (ETF): Established in 2005, the Texas ETF was intended to "expedite innovation and commercialization of research, promote a substantial increase in high-quality jobs, and increase higher education applied technology research capabilities."[36] Companies with disruptive technologies were encouraged to apply for funding up to $5 million. The decision process included a thorough vetting process (technology, IP, and

commercial potential), which added significant credibility when seeking future investments. The funding mechanisms were very favorable from the companies' perspective and typically took the form of equity. (It is no longer available.)

- Kentucky SBIR/STTR Matching Funds Award[37]: The purpose of the program is to foster job creation and economic development in Kentucky by increasing the competitive position of small businesses to attract SBIR/STTR funding. This is accomplished by providing matching funds to companies that have been granted a federal SBIR/STTR program, phase I or phase II, in one of the state's identified focus areas. Companies can receive up to 100% of the amount of the SBIR/STTR award (with some limitation) and may receive up to a total of five such awards. The application is not subject to vetting (other than ensuring that certain criteria are met), and the funds are provided in the form of a grant.

Although these programs vary widely, they typically have several attributes in common:

- The majority of the funding provided is to be used within the state that makes the award. In fact, companies that move out of the awarding state may be obligated to repay the monies upon so doing.
- The programs typically focus on commercialization, not basic research. The states are investing in the company with the hope that jobs, and taxes, will be created in the relatively near future.
- The funding may be provided as a grant, loan, or convertible debt. The entities that run these programs typically structure the deals so that they do not hinder or preclude future investments.
- Funds often are provided on a first-come, first-served basis, with a fixed amount of funding allocated to the program. As such, meritorious applications to these programs can go unfunded if the program exhausts its prescribed dollar allocation (e.g., toward the end of the fiscal year).
- There is one potential problem with state-run programs. In certain states, the legislation for the program may not provide sufficient privacy protection for documents submitted for consideration. Before applying for one of these programs, and before submitting any written reports, a device developer must fully understand what access to documents is available to interested parties using the Freedom of Information Act (FOIA).

Other than potential FOIA issues, these state-run programs are valuable. Companies need unrestricted money to find customers, market their products, and seek potential investors; other sources of funding, such as SBIR/STTR, are limited in their ability to support such activities. Thus for companies that seek to commercialize a product that results from R&D activities, these funds can be valuable. However, the award amounts are typically insufficient to bring a product, especially a medical device, to market on their own.

Other Sources of Funds

There are several other possible sources of funding for start-up businesses. Although these sources typically do not have the financial resources to fund a company from inception to first revenue, they can provide easy access to cash and other useful expertise.

Friends, Family, and Fools

Entrepreneurs often turn to their friends, families, other people they know, and credit cards to help fund the early stages of a business. These individuals typically invest because they personally know the entrepreneur and trust that he or she will provide a return on their investment. Unlike angel investors, these individuals are not required to be high–net worth individuals. However, it is critically important that such transactions be managed properly, with appropriate legal documentation and signatures.

Foundations, Not-for-Profit Organizations

Organizations whose mission is aligned with the company's product development efforts can potentially provide assistance. In some cases, the assistance may be other than cash, because some not-for-profits are restricted in their ability to finance for-profit businesses. However, these organizations typically have extensive networks of like-minded people with whom they can share information about the entrepreneur's efforts, which can lead to investments and other opportunities.

Commercial Banks

Commercial banks rarely provide loans to start-up businesses because collateral is required to secure the loan. Unless the entrepreneur is willing to collateralize his or her own assets, such as a house, there is rarely anything of bank-accepted value within the business to offer as collateral.

Figure 38.2 overlies a product's life cycle with the typically available sources of funding for the particular stage of development. The dollar values shown provide guidance about the typical order of magnitude of the funding. The light blue shaded section, that period of time during which cumulative profits are negative, is often referred to as the "valley of death."

Angel and Venture Funding

Angel investors and venture capital (VC) firms are potential sources of capital available to entrepreneurs trying to start a company. Angel investors (also known simply as angels) are high–net worth individuals who invest their own money into companies. Often angels have domain expertise or a personal interest in the technology being developed. Although the magnitude of angel investing in the United States is large, estimated to exceed $23.3 billion in 2010, individual angels, or angel groups, typically do not invest more than several hundred thousand dollars into a single firm. Due to the high costs associated with bringing a medical product to market, angels are not typically well equipped to provide substantial assistance to entrepreneurs in this field. Thus the remainder of this section focuses on venture capital.

A venture fund is a private equity investment entity that invests capital in companies on behalf of third-party investors. Usually structured as an LLC or a general partnership, VC firms receive investment capital from limited partners, be they

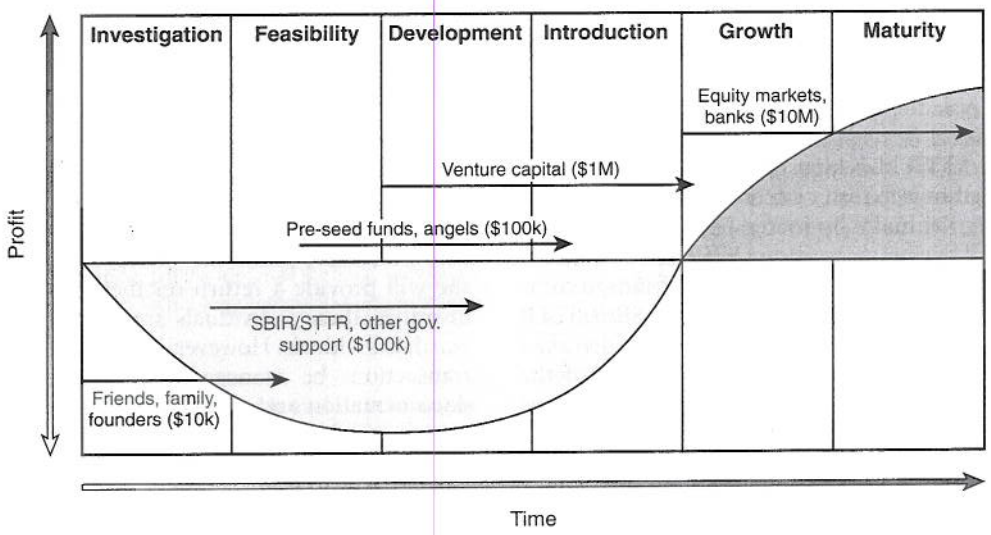

Fig. **38.2** The life cycle of a start-up company, showing stages of development and typically available funding sources. *SBIR,* Small Business Innovation Research; *STTR,* Small Business Technology Transfer.

	Pre-Deal Capitalization Structure				Class B Preferred Units		
	Common shares	Common options	Pro forma units	Pro forma ownership	Preferred issuance	Pro forma units	Pro forma ownership
Entrepreneur	10,000,000	–	10,000,000	100.0%	–	10,000,000	66.7%
Venture capitalist	–	–	–	0.0%	5,000,000	5,000,000	33.3%
Total	10,000,000	–	10,000,000	100.0%	5,000,000	15,000,000	100.0%

Fig. 38.3 Simplified capitalization table showing the change in percentage ownership upon accepting an investment.

high–net worth individuals or large financial institutions or some combination of the two. VC firms typically make investments in exchange for company shares, that is, equity in the company is exchanged for capital financing from the venture capitalist.

The exact number of shares that the VC firm receives for the cash investment is determined by what is called the *pre-money valuation* of the given company. The pre-money valuation is a negotiated value of the company's intrinsic value before taking money from the VC firm. If the VC firm and the company agree that the company is worth $10 million before the investment (i.e., the pre-money valuation is $10 million), and the amount of invested capital is $5 million, then the VC firm is effectively buying 33% of the company. By putting $5 million into a company that is worth $10 million, the post-money valuation of the company is $15 million. More simply put, $5 million added to $10 million equals $15 million; $5 million divided by $15 million equals 33% of the company (**Fig. 38.3**).[38]

Accompanying the capital that entrepreneurs can receive from VC firms is the experience that venture capitalists can offer to start-up companies. For immature companies, VC can provide the added benefit of the managerial, technical, and industry-based expertise of the venture capitalists. For medical device companies specifically, the venture capitalist may help the entrepreneur navigate through the complex regulatory approval process, set up clinical trials, understand the reimbursement coding system, establish a manufacturing relationship, ensure timely and complete filing of IP protecting patents, negotiate distribution contracts, or develop a go-to-market strategy to name just a few of the "bonuses" that the ideal VC firm can offer to the entrepreneur.[39]

The timeless VC adage in the medical device space goes something like this: every entrepreneur has impenetrable IP and every venture capitalist promises to aid the entrepreneur to surmount every hurdle during the process of taking a product to market. The truth of the matter usually lies somewhere in between the two.

What Equity Investors Are Seeking

One of the first hindrances to receiving VC is getting the attention of a venture capitalist. The best means to find a venture capitalist is through personal contacts who can then recommend the inventor and thus personalize the introduction. A trusted contact can break down even the strongest of barriers. Another means to meet a venture capitalist is at a conference. The last method is the "cold call" or "cold email," in which the venture capitalist is contacted without a formal introduction. The venture capitalist is thereby introduced to the company or idea for a company in an impromptu and extemporaneous way. (A list of venture capitalists that focus on medical devices can be located at the following website: www.devicelink.com.) David Lawee, the founder of Mosaic Venture Partners offers these tips for getting in the door:

- It dramatically improves your chances to come in through a trusted reference.
- You have to be savvy about who those people [are]...not to listen to everybody and say, "Oh, that guy's a trusted

referral." If you associate with someone who is not considered to be credible, then you get tainted by that.
- There is so much available on the Internet. Go out, read up, and learn about the market. Figure out how you're going to get to the influencers. We do that all the time for our companies. You need to do that...it's just a normal business skill.[40]

During the initial contact phase, it is customary to provide the venture capitalist with an executive summary or a "one-pager" that summarizes the company. The one-pager is ideal because it forces the entrepreneur to include only the most pertinent information that relates to the device in a "one page only" format. After sending the one-pager and arranging a conference call or an in-person meeting, it is imperative to have a solid investor PowerPoint presentation. This presentation not only helps guide the company during the story-telling process, but also shows the VC firm how detail-oriented and streamlined the company truly is.

Most venture capitalists target medical device technology companies at a specific stage, be it early stage (i.e., pre-FDA approval) or late stage and post-FDA approval (i.e., market launch). Some venture capitalists are stage agnostic and will entertain entrepreneurs at any stage in the development cycle.

The goal of VC investing is to make money on a calculated risk investment. The goal, as novel as it may sound, is to invest as little as possible and to generate as high a rate of return as possible. Buy low, sell high. All venture capitalists have their own investment thesis, but certain investment metrics do exist. Following is a general list of the basic investment criteria of a venture capitalist:

- Unmet clinical need
- Large uncrowded market
- Strong intellectual property
- Clinical and regulatory process
- System and physician economics
- Established reimbursement protocol
- Distribution and sales strategies
- Experienced management team
- Multiple on invested capital
- Overall cash return on investment

This list, if thoughtfully addressed by the medical device company in question, will help guide the venture capitalist's decision-making process. The goal of the start-up company is to put together a clear presentation that shows that the device is novel and meets an unmet need for a specific patient population. With that in mind, the entrepreneur must show how this device is a major advancement over existing technology and that it fulfills a truly unmet clinical need in a market that will generate significant returns.[41]

When the market is considered, the saying is "the bigger, market, the better." Unfortunately orphan diseases often are excluded after a market-based analysis. Some big markets include the most common disease pathologies such as diabetes, congestive heart failure, obesity, or sleep apnea.

Strong intellectual property is the *sine qua non* of VC investing. Patents protect an investment and in essence are the true assets of a start-up company. Because patent assessment requires real dollars and cents in terms of costs for legal review, this part of the due diligence process is often the last step after a letter of intent, or financial term sheet, is extended to the company.[42]

The clinical and regulatory process is one of the many hurdles that entrepreneurs must leap over on the path to taking a medical device to market. This process, and indeed it is a process, requires a deliberate and well-executed strategy when dealing with the FDA. Whether the company is filing a 510(k) or a PMA, the clinical trials that will support the FDA filing require thoughtful planning, careful selection of sites and principal investigators, and clearly defined endpoints and protocols. The choice of the PMA or 10(k) mechanism can be important because most recalls are of medical devices originally cleared through the 510(k) process or were considered of low risk and so exempt from review.[43]

When determining the economics of a medical device, the venture capitalist considers the micro- and macro-effects that the product will have on the system. Devices often are used directly by doctors or other medical practitioners. When analyzing a device, the cost to the doctor, namely the physician economics or micro-effect, must be considered in the grand economic picture. With respect to the macro-effect, the venture capitalist considers the costs to the system as a whole, for example, does the device increase office throughput or reduce operating room time? Because of the American third-party payer system, venture capitalists must consider the reimbursement rate of a medical device. Devices are paid for as part of a Diagnosis-Related Group (DRG) hospital code, through a Current Procedural Terminology (CPT) code, or by the patient him- or herself (an out-of-pocket expense). The process to establish a new CPT code is a lengthy (greater than 1 year) and exacting process that relies on careful filings and ultimately on sales generated from the device. The venture capitalist will consider the true "purchaser" of the device when evaluating a device.

When it comes to distributing and selling a device, the venture capitalist will consider the marketplace and the big players in the given clinical space. Because of established distribution channels, large medical device companies can easily add a new product to their sales representatives' "bags" and effectively blanket the country with the device in question. Unfortunately, a fledgling company does not have the wherewithal or the resources to emulate this national or global approach. The venture capitalist will consider the competitive environment during his or her analysis and weigh the different sales strategies.

How intimately venture capitalists work with their portfolio companies will determine how important the vetting of the management team's biographies is to them. In the end, the shepherding of portfolio companies through the entire process will require intense interaction. The better the communication process is, the more successful the experience will prove to be. Hardworking and assiduous people often generate successful outcomes. The returns that a venture capitalist looks for in its investment process are based largely on the methodology of the specific VC firm. In the end, a patent-protected device that addresses a disease state with a large market and that can be produced with high gross margins and low operating costs is the venture capitalist's four-leaf clover.

Pros and Cons of an Equity Investment

The pros and cons of taking on an equity investment lie in the locus of control. Control comes in two forms: financial and administrative. Before taking money from a venture capitalist, the entrepreneur has 100% control over his or her company.

The decision making is not diluted by a board of directors and is solely in the hands of the founders. Once the company decides to take on capital from a venture capitalist, the power structure of the company changes significantly. In exchange for the risk of their investment, the venture capitalists gain significant control over company decisions, in addition to a significant portion of the company's ownership (and consequently value).

The key to ensuring a safe journey lies in shrewd negotiation of the investment documents. Every line in every one of the investment documents, from the purchase agreement to the shareholders' agreement, is written for a reason.[44] To ensure that no surprises arise, seasoned legal representatives should scour the documents and negotiate the most favorable terms possible. The list of problems that can arise from poorly negotiated documents is limitless, so the enterpreneur must be keenly aware of all the pitfalls and windfalls that exist in the legal contracts.

The pros of taking on VC money depend upon the venture capitalist in question. Before taking money from a given venture capitalist, the venture capitalist should be asked for permission to contact some of their portfolio company chief executive officers (CEOs) or general managers (GMs). A transparent venture capitalist will not find anything amiss with this request and should facilitate this process. A good firm has nothing to hide. If red flags emerge from these conversations, the answer to the question of whether or not this venture capitalist will add value on top of his or her equity investment should be apparent.

If the venture capitalist receives positive reviews, the ideal venture capitalist will buttress the management team with expertise in any number of medical device-related areas. Suffice it to say, a seasoned VC firm will offer its experience in the field of medical devices, its contact lists, and the overall expertise of its team, and so ensure that capital will be coupled not with a loss of control but a gain of a valued resource.

The Equity Investment Process

After a phone call or an in-person investor PowerPoint presentation, the venture capitalist will perform due diligence on the company based on the interest level generated by these interactions. The key to getting the attention of the venture capitalist is a clear presentation that hits on the key parameters that venture capitalists consider important to make an equity investment. Initial due diligence can either precede or come after another conference call or another in-office meeting. The number of the calls and meetings varies from firm to firm, but the average inclusive number probably exceeds three (calls and meetings). The venture capitalist also may supplement information requests and in-person demonstrations by the company with calls to physicians and other trusted experts in the given field. A typical due diligence binder that the venture capitalist will request may include any of the following documents:

1. Financial plan and top line assumptions for the plan
2. Milestone chart reflecting key milestones of the plan
3. Term sheet proposal
4. Investor presentation
5. Regulatory process
6. Management biographies
7. Organization chart
8. Patent family tree
9. Summary of preclinical studies
10. Summary of clinical trial protocols
11. Clinical trial contacts
12. Explanation or overview of device
13. Capitalization table
14. Market model
15. Indications for gold standard competitor
16. Competitive grid
17. Clinical literature review
18. Clinical literature articles

At this stage in the investment algorithm, a venture capitalist will decide whether to extend a letter of intent, often referred to as a *term sheet*. This letter of intent will clearly define the investment parameters of the venture capitalist, namely, the pre-money valuation, the amount of invested capital, whether or not warrants are to be a part of the transaction, the tranching of the investment, and any milestones that the company must meet to receive the different investment tranches. ("Tranche" is French for a slice, so if a venture capitalist decides to invest $6 million, it may provide the investment in three $2 million tranches.) The letter of intent also usually defines the capitalization structure of the company and the terms of the stock investment—conversion, voting rights, redemption rights, antidilution protection, liquidation preference, and first-offer rights. The rest of the letter of intent defines the closing conditions, the transactions fees, and the legal and confidential nature of the agreement.

After the so-called "doctor calls" and the negotiation of the letter of intent, the legal evaluation of the company's IP is usually the last step in a VC firm's due diligence process because of the high cost of IP attorneys' fees.

If he or she decides to pursue an investment, the venture capitalist will send a letter of intent to the company with a monetary valuation of the company. From this starting point, the negotiation between the company and the venture capitalist begins. Ideally, the terms on either end meet somewhere in the middle about the valuation and the acceptable terms for the transaction to occur.

Conclusion

To bring a novel medical device to market is a challenging proposition. The range of activities that need to be successfully managed range from understanding the clinical issues to developing an engineered device to raising capital to complying with federal regulations to eventually selling the product. Despite the challenges, this is a process undertaken by people on a daily basis because of the potential rewards. The single most important fact to remember is that others who have done this before are available, sometimes at little to no cost, to assist new inventors in their endeavors. Therefore, one of the most important activities in which a new entrepreneur should participate is networking. Networking provides the opportunity to learn about resources available and lets others learn about the new project. Through networking it is possible to obtain recommendations for service providers, find employees, and identify people who can serve on a board of advisors.

Regardless of where an enterpreneur lives, there are local resources that can provide assistance. Most every city has a chamber of commerce,[45] an organization whose focus is on the local business community. Chambers typically have regularly scheduled meetings, which are usually great places for networking. They also offer a range of services, such as providing group insurance, that may be of value to small businesses. In addition, many chambers have SCORE offices,[46] business counseling and mentoring organizations, another invaluable resource for startups.

Many cities, or regions, have economic development corporations, typically public-private partnerships focused on growing businesses. Services offered vary widely, but some offer business incubator space, accelerator programs, and/or consulting services for entrepreneurs. All states have statewide economic development corporations that establish programs (such as those discussed previously), provide tax incentives, and a broad range of programs to assist businesses.

All states also have small business (and technology) development centers.[47] These organizations provide counseling, training, research, and advocacy for small businesses. The program, run jointly with the federal Small Business Administration, typically provides everything from classroom learning to one-on-one coaching.

The bottom line is this: starting a business and working to make it successful is an extremely rewarding process. In so doing, the entrepreneur enriches himself or herself, his or her community, and in the case of medical devices, society as a whole. Although challenging, the resources available to entrepreneurs are greater than ever, and make now the best time to start a business.

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VII Chapter 39

Engineering Issues

Brett Trimble and Jens Bracht

Introduction

History and Background

By most accounts the modern era of neuromonitoring began in the 1950s with reports of continuous intracranial pressure (ICP) measurements in humans by Janny et al.[1,2] ICP was measured by connecting a strain gauge pressure transducer to a fluid-filled tube connected to a catheter with its distal end implanted in the patient's cerebral ventricle. The use of a strain gauge, as opposed to a manometer, to measure pressure made ICP monitoring safe, easy, and accurate. The frequency response of the sensor and associated electronics was sufficient to allow visualization of the pulsatile ICP waveform. In addition periodic measurements could be plotted over time, leading to the discovery of the well-known and clinically useful Lundberg waves. Continuous ICP monitoring has become the cornerstone of critical care monitoring for patients admitted to neurocritical care units (NCCUs).

From an engineering point of view, it is interesting that the application of a simple electrical sensor and analog electronics resulted in a significant improvement in clinical practice. This is a pattern that has repeated itself in the years since Lundberg's original work in the 1960s. The remarkable developments in electronics and sensing technologies driven by the computer, telecommunications, and aerospace and defense industries have been applied to many aspects of medicine including monitoring devices used in neurocritical care.

Clinical Background

An examination of engineering issues associated with neuromonitoring devices must be made in the context of the goals and challenges of neurocritical care. Neurocritical care patients commonly suffer from traumatic brain injury (TBI), from neurovascular diseases such as subarachnoid hemorrhage, or have undergone a neurosurgical procedure such as resection of a brain tumor. In addition to the original injury or disease, patients are at risk of "secondary" injury because of the unique nature of the head and brain. One of the primary goals of neurocritical care is the prevention of these secondary injuries. The purpose of monitoring equipment used in neurocritical care is to enable the clinician to identify signs and symptoms of the primary disease, to warn of impending secondary insults, and to help judge the efficacy of treatment.

Because the brain is encased in the rigid skull, there is limited room for the brain to swell when injured. Left unchecked, swelling (edema) can lead to serious morbidity or death. For this reason ICP monitoring is important in neurocritical care. Nutrients such as oxygen and glucose are supplied and waste products removed from the brain through the blood circulation. Although the brain is a relatively small organ at 2% of body weight, it receives 20% of the body's blood flow and accounts for 20% of oxygen and 25% of glucose consumption.[3] Significantly, the brain does not store oxygen. Alterations in blood flow are common in neurocritical care patients, and there is much interest in monitoring blood flow in both the large vessels leading to and from the brain and the microvasculature within the brain parenchyma. Systemic blood pressure is commonly monitored because it is the driving force for cerebral blood flow (CBF). The concentration of carbon dioxide (CO_2), which is a powerful vasodilator and affects CBF is indirectly monitored in the expired breath. CO_2 also has been monitored directly in the brain. Oxygen tension can be measured in both the circulation and in brain tissue. The oxygen saturation of systemic blood is routinely monitored, and estimates of regional saturation of cerebral blood also are possible.

It is common for alterations in cerebral metabolism to occur in neurocritical care patients. The brain normally produces energy in the form of adenosine triphosphate (ATP) through the Krebs cycle; oxygen and glucose are necessary for this ATP production. When cerebral metabolism is disturbed, for example, by a lack of oxygen availability, the brain relies more on anaerobic glycolysis that produces less ATP. Under these conditions, brain cells may not function normally and may even lose structural integrity.[4] This condition is sometimes called *hyperglycolysis*. This condition as well as other metabolic disturbances can be inferred by various chemicals released by the brain. A portable analyzer can test samples collected from the interstitial fluid by dialysis probes implanted directly in the brain to determine the concentration of the chemical in question. The clinical utility of these measurements is the subject of significant research.

Neuromonitoring Systems: An Engineering Prospective

The Ideal Monitor

The ideal monitoring system would be noninvasive, provide continuous information, interrogate the entire brain, present the information in a way that is easily understood, be compatible with other monitoring and imaging systems including magnetic resonance imaging (MRI), take up little or no space,

meet all regulatory requirements both medical and technical, and cost very little. Few if any currently marketed devices meet all of these requirements. The following sections describe the basic components of most common existing monitoring systems, give an overview of the types of sensing techniques that are or have been used, and assess the pros and cons of each technique.

Most monitoring systems used in neurocritical care consist of a sensor in contact with the scalp or directly implanted into the brain, some kind of fixation device that keeps the sensor in place during the monitoring period, connecting cables, and a stand-alone electronic monitor to operate the sensor and display data or connect to a bedside monitor.

Fixation Techniques

Fixation is an extremely important aspect of monitoring systems. Fixation systems must ensure consistent alignment or contact between the sensor and the patient. Two primary fixation techniques are used for indwelling sensors: bolt fixation and tunneling. Most indwelling sensors take the overall physical shape of a long slender cylinder usually referred to as a *catheter* or *probe* with the sensor located at the tip of the probe (**Fig. 39.1**).

Bolt Fixation

The bolt device is composed of a short metal cylinder with self-tapping threads at one end and some kind of compression fitting at the other end. The bolt is usually threaded to a depth of approximately the thickness of an adult skull of approximately 0.7 cm. The thread pitch is usually sized such that at least three or four fully formed threads will be in contact with the skull with the bolt in place. If the thread pitch is too large, not enough contact is made by the thread crests to ensure a secure and leakproof fit. The lead-in threads are usually tapered in a manner similar to pipe threads with the crest height of the initial one to three pitches smaller than the diameter of the twist drill used to cut the insertion hole in the skull. The compression fitting must resist axial movement of the probe and provide a leakproof seal around the outer surface of the probe. The maximum compressive force that can be exerted must be limited to an amount that will not damage the probe. Providing strain relief at the junction between the top of the bolt and the probe is a good practice. The ultimate strength of both the bolt and probe in bending and tension must be carefully considered because the probe and bolt often are subjected to significant loading when the probe or a connecting cable is inadvertently pulled when it catches on a fixed object during patient transport, the patient falls out of bed with the cable wrapped on the bed frame or other stationary object, or the patient pulls on the probe in a semiconscious state. It is far better for the bolt or probe (outside the patient) to break than the bolt to break in the skull (**Fig. 39.2**).

Tunneling

Perhaps the oldest fixation method is tunneling. Tunneling refers to the surgical technique of routing an elongated catheter under the scalp toward the insertion site. This method has the advantage of good fixation to the patient using stitches in the scalp and better infection control than simply routing the catheter out of the scalp directly over the insertion site. This technique is commonly used with fluid-filled ventriculostomy ICP monitoring. It also has become common for transducer-tipped probes to be affixed to the patient via tunneling. It is important to recognize that the probe must be capable of making a right-angle turn into the skull into the insertion site under the scalp without being damaged. Because the connectors on the proximal end of most probes are too large to be tunneled under the scalp, many of these devices are not

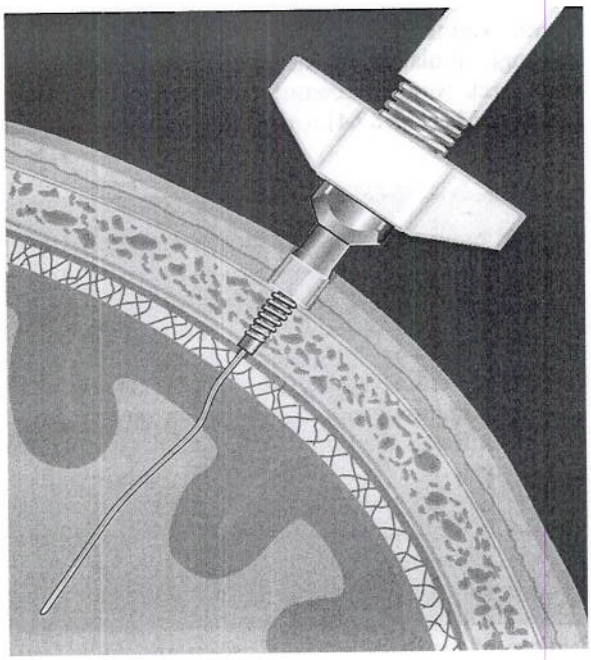

Fig. 39.1 **Bolt fixation device.** Licox oxygen sensing catheter and fixation bolt. *(Used with permission of Integra LifeSciences Corporation.)*

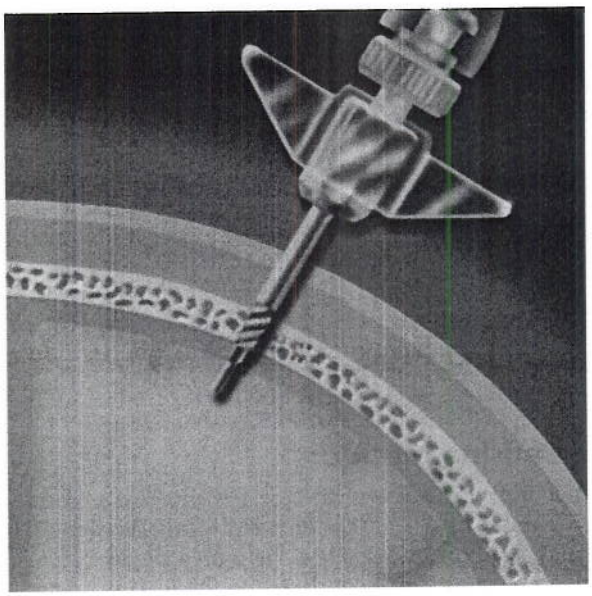

Fig. 39.2 **Bolt fixation device.** Camino intracranial pressure bolt in situ. *(Used with permission of Integra LifeSciences Corporation.)*

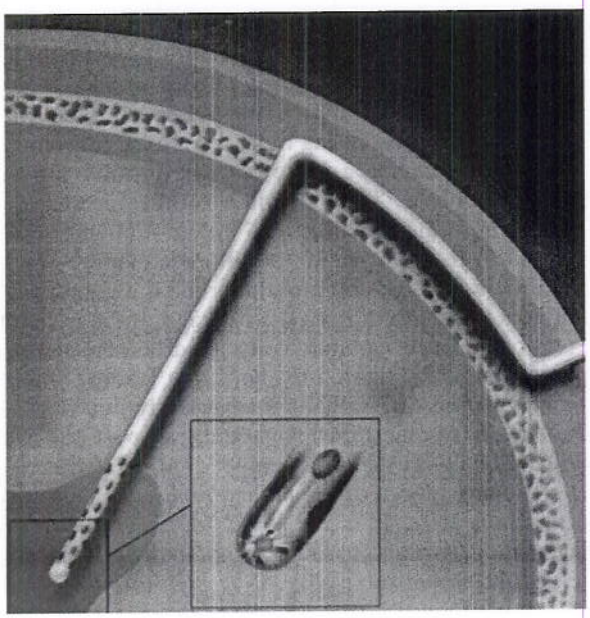

Fig. 39.3 Tunneling fixation. Ventrix intracranial pressure catheter tunneled under scalp. The inset shows the sensor in the tip of the ventricular catheter. Note the shape of the probe tip (bullet-like) that limits tissue injury during insertion. *(Used with permission of Integra LifeSciences Corporation.)*

tunneled per se but are routed through a plastic sleeve that has itself been tunneled under the scalp. This "tunneling sleeve" usually takes the form of a plastic tube connected at one end to a solid trocar. After the sleeve has been tunneled under the scalp, the trocar is cut from the sleeve and the catheter is passed through the sleeve toward the insertion site. The tip of the catheter is then implanted and the catheter and/or sleeve are sutured to the scalp via loops (**Fig. 39.3**).

Other Fixation Methods

Noninvasive monitoring devices such as electroencephalograph (EEG) electrodes, near infrared (NIR) oximeters, and transcranial Doppler (TCD) probes are affixed by hand, by mechanical means, or by the use of some kind of adhesive tape–like substance. Heavy devices that are not usually used to make continuous measurements such as TCD transducers are simply held to the head by the technician or are sometimes fitted to a device that looks like an eyeglass frame. Lighter transducers like EEG electrodes or oximeter leads usually are held in place by adhesive patches. The adhesives used must not irritate the skin during monitoring durations of up to several days, must not cause hair to be removed when the patch is removed, and must securely hold the transducer in place over the monitoring period.

The Bedside Monitor

Most if not all neurocritical care patients are connected to bedside monitors (BSMs). The BSM collects signals from external monitors and displays them on a single screen. Generally each parameter is connected to the BSM via detachable "modules" that are part of the BSM and accept analog or serial input from an external monitor. Each module is tailored to a

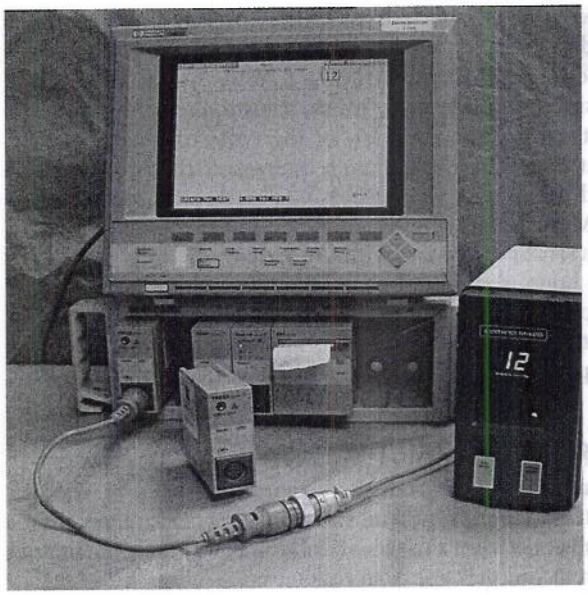

Fig. 39.4 Hewlett-Packard bedside monitor connecting cables and Camino monitor. *(Used with permission of Integra LifeSciences Corporation.)*

specific parameter type such as pressure or temperature. Commonly displayed parameters include electrocardiogram (ECG), heart rate, temperature, blood oxygen saturation, cardiac output, and mean arterial blood pressure among other options. Most physiologic pressures such as arterial pressure, pulmonary artery pressure, and pulmonary capillary wedge pressure are monitored using strain gauges. BSMs are therefore designed to provide electrical excitation of the strain gauge and to interpret pressure from the electrical signals returned form the strain gauge. Neurologic-related parameters, other than ICP signals measured by fluid filled systems, are generally not included in the current generation of BSMs. Devices that measure parameters that are not included as standard features of the BSM commonly connect to it via analog strain gauge emulation or by serial means when available. Cable connectors must accommodate the various makes and models of BSMs (**Fig. 39.4**).

Primary Sensors

The injured brain can be a difficult sensing environment. In particular intracranial hemorrhage of one form or another results in free and clotted blood both of which can damage or confound many types of indwelling senor elements. Blood or large proteins in the cerebrospinal fluid (CSF) also can deposit on indwelling sensors and so damage or confound them. Monitoring durations may continue for several days and increase the chances that blood, blood clots or proteins may deposit or form on implanted sensors.

Invasive catheters must be stiff enough to be pushed past an opening in the dura mater and into parenchyma anywhere from a few millimeters to several centimeters, such as with a ventricular catheter. However, once implanted, catheters should be flexible enough to impart the least amount of force on the tissue if overloaded. The hair, scalp, and skull of varying thickness are all factors to account for when using noninvasive monitors.

Many primary sensor technologies have been used in neurocritical care monitors. Electrical, optical, chemical, and ultrasound are some of the broad categories.

Electrical Sensors

Strain Gauge

Doped silicon piezoresistive strain gauge sensors are used commonly to transduce ICP. Miniaturized versions can be placed in the distal tip of catheters, whereas larger versions are placed outside the head in fluid communication with the ventricle or less commonly the subarachnoid space. Both full- and half-bridge devices, with and without temperature compensation, are common. These devices are accurate and reliable and in the larger sizes low cost, because these larger devices are manufactured in large quantities for use in peripheral arterial line blood pressure monitoring. The use of the strain gauge to sense pressure has the added advantage that BSMs are designed to operate them directly; this eliminates the need for complicated electronics between the sensor and the BSM. The wire bond junctions must be protected from corrosive environments, often with low modulus adhesive coatings. The chip must be insulated from mechanical strain other than that imparted by what is to be measured, such as ICP. This is a difficult design requirement, and much intellectual property and many trade secrets revolve around this issue (**Fig. 39.5**).

Polarographic Electrodes

Electrochemical "polarographic" electrodes are used to measure oxygen tension in the brain parenchyma. A metal cathode and anode and electrolyte solution are contained in an oxygen-permeable plastic tube. Oxygen molecules that have diffused through the probe wall react with water at the surface of the cathode to produce hydroxide ions. Free electrons then are liberated, causing current flow between the cathode and anode. This current is sensed by the monitor and is proportional to the partial pressure of oxygen in the tissues in contact with the probe. This method has proven to be accurate and reliable and does not require complex optical or electronic devices for operation (**Fig. 39.6**).

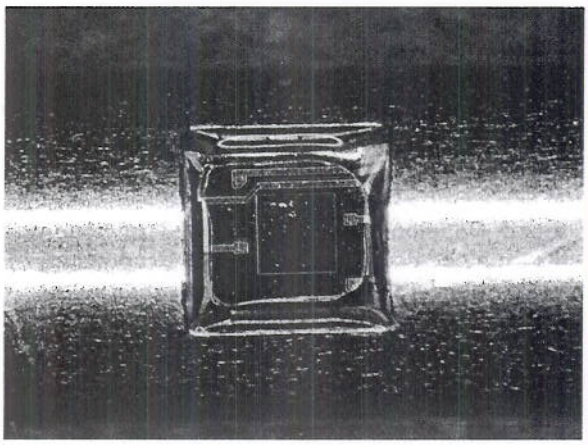

Fig. 39.5 Strain gauge pressure transducer within NeuroSensor ICP/CBF probe. *ICP/CBF,* Intracranial pressure/cerebral blood flow. *(Used with permission of Integra LifeSciences Corporation.)*

Electroencephalogram

EEG sensors are simple electrodes typically connected by a single wire to one side of a differential amplifier with the other side connected to a common reference. Arrays of up to 256 leads are common and can measure the electrical activity of the brain through the scalp, the dura, pia mater, or directly in the cortex. EEG monitoring is a very mature technology, but there have been several recent improvements including noise suppression and signal processing techniques. In addition, improvements in analog electronics and the advent of digital signal processing (DSP) have made EEG monitoring more reliable and easier to understand for the clinician. For example, useful time and frequency domain transformations are now easy and inexpensive to implement with commercially available DSP chips and software. Because of these technologic advances, continuous EEG is used more frequently in NCCUs, and its use has provided insight into physiologic effects of brain injury and how seizures themselves may cause secondary injury.[5]

Optical Sensors

Intensity Modulation

Many optical methods have been used to sense neurologic parameters such as pressure, oxygen tension, and blood oxygen saturation. Most indwelling optical sensors rely on a fiber-optic connection to optical components outside the head. Optical ICP sensors use a primary mechanical sensor and an optical proximity detector to transduce pressure. One commonly used device makes use of a miniaturized thin-walled bellows closed at one end as the primary transducer. The intensity of light reflected by the closed end of the bellows from one optical fiber to another is used to sense the bellows' position. The geometry of the reflections modulates the intensity of the returned light signal, which in turn is proportional

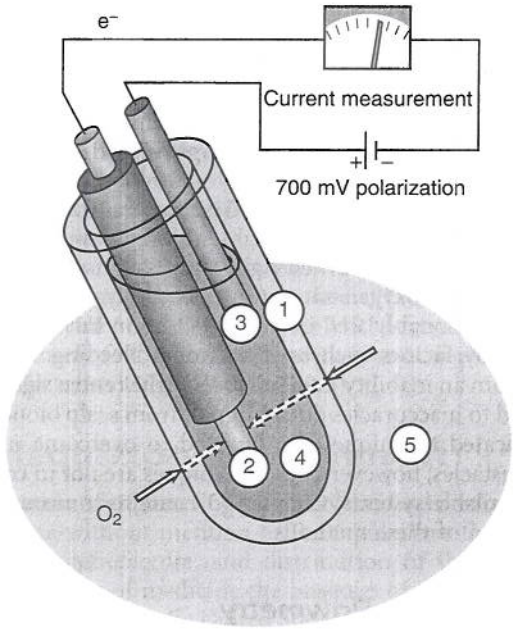

Fig. 39.6 Licox oxygen sensor that uses polarograph electrodes. *1,* Oxygen-permeable plastic tube; *2,* cathode; *3,* anode; *4,* electrolyte solution; *5,* tissues in contact with probe. *(Used with permission of Integra LifeSciences Corporation.)*

to pressure. The only optical components used are the optical fibers, a light-emitting diode (LED), and two photodiodes, all of which are contained in the probe.

Interferometer Proximity Detection

Another optical pressure sensor device used to measure ICP uses an interferometer to measure the depth of an optical cavity formed by a silicon diaphragm bonded over a cavity etched in a small cylinder of borosilicate glass. The cavity is vented to atmosphere on its proximal side; therefore, changes in cavity depth caused by displacement of the silicon diaphragm are proportional to ICP. This sensor has the advantage of being formed of all glass materials, which reduces the effects of differential thermal expansion or water take-up causing apparent pressure changes not due to a change in the patient's ICP.

Fluorescence Quenching

Optical sensors have been used to measure oxygen and other parameters in the brain using the technique of fluorescence quenching. Typically silicone room temperature vulcanizing (RTV) adhesive is applied to the end of an optical fiber. The RTV is doped with dye that fluoresces at a specific wavelength. The intensity or duration of the light signal generated by the fluorescence also is altered by the presence of a target molecule such as oxygen. The fluorescent dye also can be immobilized by applying it to porous glass microbeads. The rate of fluorescent decay when the lamp or LED used for excitation is turned off is used to measure temperature in some devices. These systems can be reasonably accurate and cost effective.

Spectroscopy

Optical techniques also may be used to measure concentration of hemoglobin and the total oxygen saturation of hemoglobin in blood. The absorption of light at convenient wavelengths in near-infrared (NIR) near the isobestic point for hemoglobin are measured and used to determine the absolute concentrations of oxyhemoglobin, deoxyhemoglobin, and total saturation in blood. The same principle is used in noninvasive cerebral oximeters to estimate regional blood oxygen saturation in brain tissues. The forehead is illuminated by two emitter-receiver pairs with NIR light at two wavelengths. The attenuation of the returned light signals is used to estimate regional blood oxygen saturation.[6] These systems appear to function reasonably well in uninjured brain but can be confounded by factors such as intracranial bleeding. They also suffer from an inability to depth resolve the return signals; this may lead to inaccuracies due to signals from scalp blood. More sophisticated techniques can be used to overcome many of these obstacles; however, these techniques are not in commercially available systems. Chapter 33 contains a more detailed description of these methods.

Laser Doppler Flowmetry

Optical methods are used to estimate blood flow in brain parenchyma. The well-known laser Doppler flowmetery technique has been used in many products over the past 15 to 20 years. The tissue is illuminated with collimated light from a laser source in the near infrared. Light is scattered by stationary structures in the tissues as well as the moving red blood cells. Light reflected by the moving red blood cells undergoes a Doppler phase shift dependent on the blood cells' velocity. This in turn causes the spectra of the returned light to be broadened by some 20 Hz to 20 kHz. This spectral broadening is used to estimate the velocity of the moving red blood cells. The intensity of the returned signal is used to estimate their concentration, and the product of the two terms, commonly referred to as *flux*, is proportional to blood flow.[7] This measurement technique is attractive because it is continuous, allows for the visualization of the blood flow pulse waves, and can be used in febrile patients. The technique, however, is not quantitative.

Thermal Diffusion

Thermal diffusion techniques are used to measure blood flow in the parenchyma. Two thermistors are located near the distal tip of a probe. Current is passed through one thermistor to raise its temperature a predetermined amount above the tissue temperature. Heat from this thermistor is transferred by both conduction and convection. The convective heat transfer is due to blood flowing past the probe. Knowledge of thermal properties of the parenchyma, the temperature rise of the thermistor, the power required to maintain the thermistor at temperature, and other factors can be used to estimate the rate of convection and therefore the blood flow near the probe tip.[8]

Other Sensors

Microdialysis

Microdialysis probes are used to collect samples of chemical substances from the interstitial fluid. The catheter is composed of a small-diameter tube with a membrane at the distal end filled with a perfusion fluid. The proximal end of the catheter ends in a collection vile. Chemicals diffuse across the dialysis membrane into a perfusion fluid inside the catheter. The probe membrane can be constructed such that chemicals of different molecular weight can be collected. The chemical of interest is collected in a sample vial connected to the catheter. The sample is then analyzed in a bedside chemical analyzer. The list of potential substances that can be measured is long, but in the clinical environment glucose, lactate, and pyruvate are the most frequently analyzed substances. Microdialysis is a excellent research tool, but its use in routine clinical practice has been limited by the intermittent measurements and need to transfer samples from the patient to the analyzer (**Fig. 39.7**).

Doppler

Ultrasound Doppler techniques are used to noninvasively measure the blood flow velocity in the large conductive vessels in the circle of Willis. The transducer head, including transducer and receiver, is positioned where the skull is thin (temporal region) and the ultrasound energy, typically using frequencies of around 2 MHz or a multiple thereof, is focused on the vessel of interest. The phase shifted return signal is used to calculate velocity. Although accurate blood velocity measurements can be made, it is harder to use as a continuous monitor because it can be difficult to maintain contact and alignment of the transducer head.

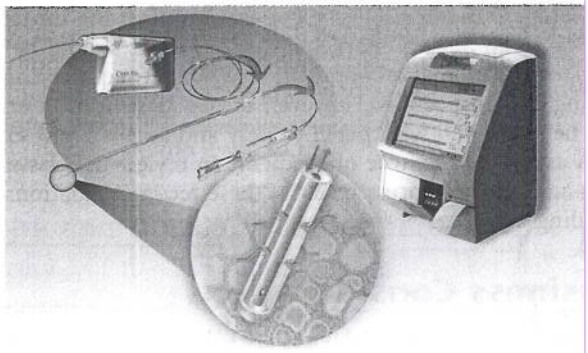

Fig. 39.7 Microdialysis system showing microdialysis catheter, pump and analyzer. *(Courtesy CMA Microdialysis.)*

Safety

Safety is a paramount consideration in the design, manufacture, and use of monitoring devices in neurocritical care. Safety hazards generally relate to the probe and sensor, ancillary components such as fixation devices, connecting cables, and the electronic monitor used with the sensor. Manufacturers of medical device products use formal risk analysis procedures to identify hazards and mitigation methods and to determine whether the residual risks after mitigation are acceptable. The list of potential safety concerns is exhaustive; the more important issues posed by neurocritical care monitoring devices are discussed in the following text.

Probe and Ancillary Components

The shape of the distal tip of implanted probes should be given careful consideration. An ogive or bullet-nose shape is probably the best and safest design. A completely blunt shape with a sharp transition between the axial tip and the outer diameter of the catheter tip is probably the worst because it tends to tear tissues during implantation. The behavior under unanticipated loading of components that are implanted in the patient, the connection to components implanted in the patient, or which secure implanted parts should be considered to limit transmission of these loads to the patient as much as possible. The methods of sealing implanted probes and fixation devices against leaks must be given careful thought to minimize the chances of infection. Materials that contact the patient must be chosen to minimize irritation and must be tested for biocompatibility, for example, per International Standards Organization (ISO)10993 Biological Evaluation of Medical Devices.

Electronic Components

Electronic monitors and cables pose their own set of safety concerns. Malfunctioning electrical devices can display erroneous data, cause burns and electrical shock, and interfere with the proper functioning of other electronic devices. Electrical safety issues such as patient electrical isolation, leakage currents, radiated emissions, susceptibility to radiated emissions, flammability, and a host of other potential safety issues are covered in the electrical safety standard International Electrotechnical Commission (IEC) 60601 *Medical Electrical Equipment—Part 1: General Requirements for Safety* and related documents. Medical devices sold in the United States, the European Union, and many other parts of the world must meet this standard as tested by an independent test laboratory such as Underwriters Laboratories (UL), Technical Inspection Association (TUV), British Standards Institution (BSI), and the like.

Magnetic Resonance Imaging Safety

An area of increasing concern is the safety of medical devices in the MRI environment. Devices made of or containing metal can translate in the scanner due to the strong magnetic field and can rotate to align with the direction of the magnetic field, imparting torsional forces. In addition, lead wires or other elongated components capable of carrying current can couple with the radiofrequency (RF) field in the scanner causing the device to heat, particularly at the distal tip. There are reports of patients and others sustaining injuries due to each of these safety issues. The American Society for Testing and Materials (ASTM) International in close cooperation with the U.S. Food and Drug Administration (FDA) has developed test standards to measure magnetically induced displacement force, magnetically induced torque, and RF-induced heating of passive implants along with a guide for MRI safety labeling.[9-11] Of the three test methods RF heating is by far the most difficult and complex. The understanding of factors that influence RF heating in the MRI environment is rapidly advancing and as such, testing requirements are in flux.[12] As of this writing the revision of the standard for measurement of RF-induced heating on or near passive implants is ASTM 2182 11a. In addition, a joint working group of the IEC and ISO has developed a test standard (TS) for MRI safety testing of active implantable medical devices (AIMDs) that is a precursor for an International Standards document. RF heating is influenced by the strength of the electromagnetic fields present in the scanner. These fields vary spatially depending on such factors as location within the RF coil and interactions between the electromagnetic fields and the device and patient. Current best practice appears to be to measure the heating of the device in a phantom within an RF coil or MRI system while controlling or measuring the electromagnetic fields to obtain a baseline understanding of the response of the device to a well-understood set of conditions. This information is then used in conjunction with computer modeling of the patient, device, and the scanner to predict heating in actual use. Regardless of the form the test method ultimately takes, it is important for devices to be tested for MRI safety and for clinicians to closely follow the MRI safety instructions provided by manufacturers (**Figs. 39.8** and **39.9**).

The Regulatory Environment

No discussion of engineering aspects of medical devices would be complete without mention of the regulations that govern the design, manufacture, and distribution of these devices. Like the practice of medicine the business of medical devices is highly regulated. In the United States the primary governing laws are contained in the Code of Federal Regulations titled Quality System Regulation.[13] This set of regulations is enforced by the FDA. The Council of European Communities Medical Device Directives of 1993 that was last amended in 2007[14]

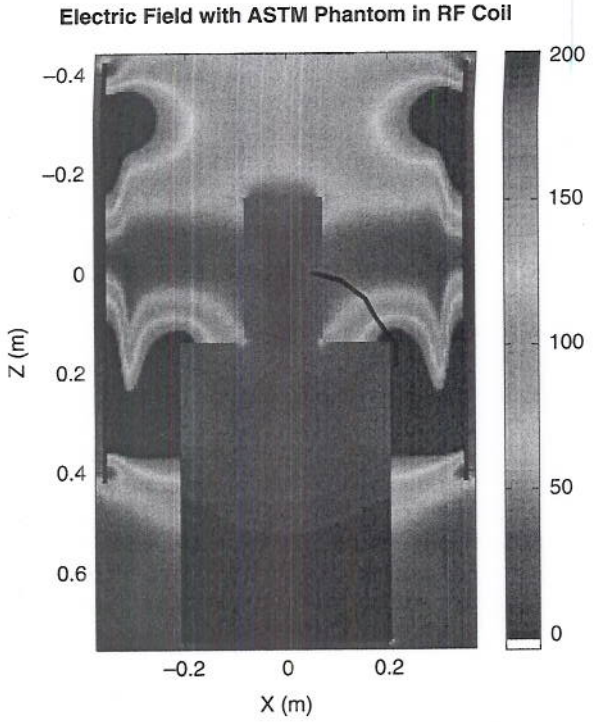

Fig. 39.8 Finite-difference time domain (FDTD) plot of electrical fields in and around American Society for Testing and Materials (ASTM) phantom within magnetic resonance imaging radiofrequency (MRI RF) coil. *(Used with permission of Integra LifeSciences Corporation 2008.)*

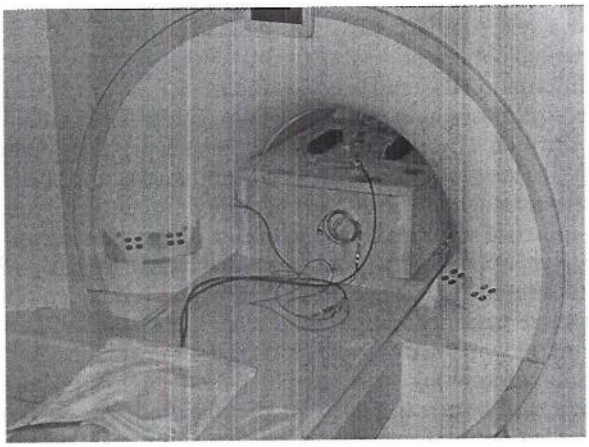

Fig. 39.9 American Society for Testing and Materials (ASTM) phantom in 1.5T magnetic resonance imaging (MRI) scanner during device MRI safety test. *(Used with permission of Integra LifeSciences Corporation 2008.)*

governs the products made or sold in the European Union (EU) and the manufacturers thereof. It is critical for engineers to understand these and many other regulations as they impact most technical decisions. Furthermore, it is important to consider these regulatory issues early in design and development to ensure that any new idea is feasible in the clinical environment before expending time and labor. At present the FDA divides medical devices into three classes according to their level of risk to a patient. There are two alternative regulatory standards: (1) 510(k) that requires the device be similar to an already marketed device (i.e., it should be low risk), or (2) premarket approval (PMA) that requires clinical testing and inspection. However, device classification errors can be associated with patient safety and recalls[15] and so the FDA asked the Institute of Medicine to review the classification and review process in 2011; these recommendations are pending.

Business Considerations

The majority of medical devices are sold by for-profit companies; therefore the decision to develop and market a medical device is in large part an economic one. Most companies apply a disciplined and analytical approach that uses one or more forms of return on investment analysis. The cost of developing the product and the costs of making and selling it are weighed against future revenue streams from sales of the product. The time value of money is always a factor in these calculations. One easy-to-understand approach is to determine the net present value of future revenues less all expenses. This estimate can be compared with competing projects or simply the interest earned by placing the same amount of money in a savings account. It is important for engineers and clinicians to understand the basic economic principals that govern how companies decide what products to develop and when to develop them. Obviously products that address a large market, are not costly to produce, command a high price, and are inexpensive and quick to develop are favored.

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Design of the Future Neuroscience Intensive Care Unit

"Superdocs," Central Consoles, Data Routing, and the Challenges in Integrating These Methods

Advances in microchip technology are occurring rapidly. These improvements will enable more refined means of data processing, storage, and acquisition in the NCCU. The ICU of the future may be a console operated system in which a central physician is the "air traffic controller" who has access to all data continuously and can thus make decisions and institute therapies at remote locations with wireless systems, possibly in a different hospital or even city (see also Chapters 4, 42, 43, and 44).[155] In central California, such systems have allowed smaller level II hospitals to continue to function with remote intensive care specialists linked in by telemedicine. Early research suggests this telemedicine approach may help improve patient outcome, in part because it can answer staffing needs.[156,157] Linked drug-device combinations or "smart systems" may automate certain functions such as administering benzodiazepines during the presence of seizure activity, venting an ICP device, or administering mannitol during ICP elevations.[158] However, there are many hurdles, including technologic and legal to overcome before such systems become commonplace.[159]

The Role of Industry

Industry is a major driving force in whether certain concepts receive the financial support to be marketed and developed. Furthermore, crossover technologic advances, such as those made with microprocessors in the computer industry, translate into new developments downstream for medical devices. Products are in a constant flux, undergoing development and replacement. The big neuroscience companies involved in neurocritical care (e.g., Integra Neuroscience-Plainsboro, NJ; Medtronic, Goleta, CA; Codman, Raynham, MA) serve as a "choke point" for the integration and commercialization of new ideas in NCCU. Development of devices sometimes depends on the potential market and return on investment rather than the engineering and clinical expertise, and there have been visionary, futuristic ideas that have not yet received the financial support required for widespread production. For example, one idea that is not yet used in NCCUs is the concept of monitoring oxidized and reduced states of nicotinamide adenine dinucleotide (NADH).[160] Alternate methods for the financial jumpstarting of ideas include SBIR grants funded by the National Institutes of Health (NIH). The SBIR program supports small businesses to stimulate technologic innovation in biomedical research (see Chapter 38).[161]

Innovation is the key to progress in neuromonitoring. This depends on the interaction between physicians, surgeons and scientists, information technologists, or engineers from many disciplines. However, legislation, at least in the United States has created intense scrutiny of the relationship between health care providers and industry. This scrutiny comes from both the public and from Congress (e.g., the Grassley-Kohl Physician Payments Sunshine Act of 2007). However, it is important to recognize there is a difference between industry-provided consultation fees and royalty revenue. Critics argue that consultation fees are often rewards for "loyal" users of a particular product, drug, or device. By contrast, royalty revenue is distributed to those who develop a particular product, that is to say, innovation is rewarded. On the other hand, the Bayh-Dole Act for universities of 1980 has catalyzed an interest by academic institutions to promote innovation because it allows universities to patent and exclusively license federally funded inventions. In turn this facilitates the translation of ideas generated on the bench to patients at the bedside that requires close collaboration between scientists, entrepreneurs, venture capitalists, and industry.[162]

Conclusion

The field of neuromonitoring is continually expanding with new developments. This chapter has covered past, present, and future techniques used to monitor patients in the NCCU. Much of the research and applications have been in TBI. Industry plays a major role in which concepts receive financial backing and ultimately end up in mainstream use. Monitors should present pertinent, online, and specific information. Furthermore, the information gathered may also facilitate an understanding of the mechanisms involved in brain injury, including TBI, stroke, SAH, and cerebral edema. This may lead to the engineering of better medicines, the production of more refined clinical trials, and the improvement of patient outcomes. Promising methods that may be used increasingly in the future include biomarkers, seizure and CSD sensing equipment, and global blood oxygen saturation analysis through NIRS, and further in the future, nanotechnology and LOCs.

Given the enormously responsive research and development environment in the modern world, the challenge to all who work in NCCU is clear; there is a need to devise new ideas and partner with industry, to advance the field of brain monitoring and improve outcome for patients. In this manner patient management can be moved from empiric to targeted stratified care and ultimately to individualized care based on genomic and mechanistic analysis.

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