Responsible Innovation in Children’s Surgical Care

SECTION ON SURGERY, COMMITTEE ON BIOETHICS, AMERICAN PEDIATRIC SURGICAL ASSOCIATION NEW TECHNOLOGY COMMITTEE

abstract

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POLICY STATEMENT
Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of all Children

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Advances in medical care may occur when a change in practice incorporates a new treatment or methodology. In surgery, this may involve the translation of a completely novel concept into a new procedure or device or the adaptation of existing treatment approaches or technology to a new clinical application. Regardless of the specifics, innovation should have, as its primary goal, the enhancement of care leading to improved outcomes from the patient’s perspective. This policy statement examines innovation as it pertains to surgical care, focusing on some of the definitions that help differentiate applied innovation or innovative therapy from research. The ethical challenges and the potential for conflict of interest for surgeons or institutions seeking to offer innovative surgical therapy are examined. The importance of engaging patients and families as “innovation partners” to ensure complete transparency of expectations from the patient’s and provider’s perspectives is also examined, with specific emphasis on cultural competence and mutually respectful approaches. A framework for identifying, evaluating, and safely implementing innovative surgical therapy in children is provided.

BACKGROUND

By its nature, surgery involves risks to patients that often go beyond the usual risks of adverse outcome associated with a diagnostic test or drug treatment. Although treatment standardization through protocols and practice guidelines is increasingly recognized as an effective harm-reduction strategy, surgeons have tended to place an equally high value on applied creativity, in recognition of a need to respond to unexpected findings at surgery, including anatomic variation. This same creativity in individual surgeons has brought forth some of the greatest advances in care in the modern era of medicine (solid organ transplantation, extracorporeal membrane oxygenation, minimally invasive surgery), advances that have often been made without clear evidence of their safety and efficacy before dissemination. Similarly, anecdotal reports...
of success of an innovative practice by a pioneering practitioner may persuade the widespread adoption of that practice before recognition of all procedural risks (e.g., Nuss procedure). 12

Surgical devices are subject to regulation by the US Food and Drug Administration (FDA) through an extensive, time-consuming, and costly process. The powerful influence of market forces discourages surgical device development for specific use in children, who represent a tiny market opportunity compared with adults, thereby severely limiting the oversight role of the FDA for device safety and effectiveness in children. 3 As will be discussed, a significant proportion of surgical device use in children represents “off label” use of a device approved for adults. There are other systems that can be used in a partial oversight role for procedures involving a surgical device or technique that has not yet been proven effective in children. Jurisprudence, for example, provides a framework that differentiates the assignment of tort liability retrospectively for patient harm caused by an inability to meet an accepted standard of care (the clinical practice pathway) from a failure to provide “enhanced disclosure” in obtaining informed consent for an innovative procedure where a lack of knowledge of all the risks exists. 4 Nevertheless, there remains an oversight gap for innovative therapy, which requires a process that can be used prospectively and has the shared objectives of encouraging innovation on the one hand while ensuring patient awareness and optimized safety on the other.

INNOVATION IN SURGERY

“Innovation” is defined as the act of introducing something new 4 or the use of a new idea or method. 5 Applied to surgery, innovation usually represents a new technology or surgical technique that involves a significant departure from existing treatment options. Innovation is driven by a combination of factors, the most important of which is the need to continually improve treatment and outcomes for patients. Although improvements in care and outcome are a foundation of all types of health care innovation, other drivers are identifiable in most cases of significant surgical innovation. These drivers include the attributes of pioneering surgical innovators who, by their nature, are creative, driven to challenge the status quo, open to serendipity, and resilient and adaptive to initial failure. Other important drivers of innovation, given the critical codependence of surgery and technology, are surgical device manufacturers and technology markets. Both may be influenced or sustained via incremental improvements by an incumbent industry leader or disrupted when a new technology competitor (often working in collaboration with an innovation consortium of investors and researchers) develops a technology or device that offers a completely novel alternative to current therapy. 6

Regulating Surgical Innovation in Children: The Role of the FDA

The FDA’s responsibility to protect the public’s health includes the regulation of devices used for surgical care. At present, the FDA plays a very limited role in the regulation of medical devices for use in children, because virtually all pediatric use represents off-label or “physician-directed” use of devices approved for adults, meaning their safety and effectiveness in children are inferred. The FDA classifies medical devices according to the risk associated with their use, and only the devices with highest risk (class III) require FDA approval before marketing. 7 Examples of class III devices include implants that support vital functions, such as prosthetic heart valves and orthopedic implants. Moderate-risk (class II) devices, including implantable vascular catheters and mesh implants, typically are cleared for use on the basis of an FDA determination that they are “substantially equivalent” to an already legally marketed device, which, paradoxically, may discourage the development of truly novel technology.

There remains an unavoidable lack of incentive within surgical device and technology markets to develop devices for specific use in children because of the comparatively small market share. With a few notable exceptions, the time and cost of shepherding class III devices through the traditional stream of safety and effectiveness evaluation before FDA approval must be borne by individual innovators and remain a major obstacle to surgical device development for children. An Investigational Device Exemption permits the use of a nonapproved device in a clinical study, provided there is institutional review board (IRB) approval, patients are fully informed of the investigational nature of the device, and there are appropriate data-safety monitoring and other quality and safety design controls in place. 8 Another alternative pathway to premarket approval is a Humanitarian Device Exemption (HDE). 9 A humanitarian use device is one that is used to treat a disease or condition that affects fewer than 4000 individuals in the United States per year. An HDE provision permits device approval if it can be shown that the device does not pose an “unreasonable or significant risk of illness or injury, and that the probable benefit outweighs the risks.” Although an approved HDE authorizes marketing of the device, there is still a requirement for hospitals to engage their IRBs in supervising its clinical use.
In 2009, the FDA Office of Orphan Products developed a special program to support pediatric device development in areas of unmet need. This program, called the Pediatric Device Consortia Grant Program, provides grant funding to consortia whose efforts will lead to market approval of devices designed specifically for pediatric (≤21 years old) use. Since this program began, a total of 8 consortia targeting new devices (including 5 focused specifically on surgical devices) for children have been funded, with evidence that these teams are making significant progress toward premarket approval.

Despite the role of the FDA in approving surgical devices, it is important to realize the FDA's limited oversight role for surgical innovation in children. As discussed later, the primary responsibility for ensuring that innovation is introduced safely and with transparency lies with the treating surgeon, working collaboratively with a committee tasked with the critical appraisal, approval, and oversight of proposed innovative surgical procedures.

**Defining Innovative Therapy**

Opportunities for treatment innovation emerge at the preclinical level, where results of experimentation suggest a potential role in patient care, and continue along the knowledge translation pathway to formal evaluation in randomized controlled trials, which offers verification that a treatment is safe and effective before its widespread implementation in humans. Although the development of new medicines follows this traditional, regulated pathway, there are only a few examples of significant surgical innovation in children that have followed this path. More frequently, changes in surgical practice have been the result of either dramatic advances or incremental improvements in existing usual practices, which, generally speaking, are not subject to any oversight other than hospital privileging, professional society guidelines, and a thoughtful conscience and desire to help patients without causing undue harm. The unavoidable “gray zone,” or “transition zone” that exists between what is clearly research and what is clinical practice represents a challenge, both in its definition and, once defined, in determining models of oversight for implementation. For the purpose of this report, what is referred to as “innovative therapy” is a procedure or technology at the interface between research and clinical care, for which special oversight that is outside the purview of both the clinical privileging process and the hospital IRB is required. The original concept and description of innovative therapy arose from the Belmont Report, which is detailed below.

In 1979, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research created the Belmont Report, which sought to establish an ethical framework for human research. The report defined “research” as an activity designed to test a hypothesis, permit conclusions to be drawn, and thereby develop or contribute to “generalizable knowledge,” whereas the practice of accepted therapy (“practice”) referred to interventions that are designed solely to enhance the well-being of an individual patient and that have a reasonable expectation of success. The report identified “experimental” procedures (which, for the purpose of this document, are interpreted as “innovative”) as those representing a significant departure from standard practice that do not qualify as research. Such procedures are intended and expected to benefit patients yet possess a degree of novelty that includes the possibility of unforeseen outcomes and the potential for generalizable knowledge to be accumulated through the collection of observational data. Procedures that are “radically” innovative (meaning their novelty is substantially different from what is done currently, making it difficult, if not impossible to reasonably estimate procedure-specific outcomes) should be made the subject of formal research initially to ensure their safety and effectiveness. Responsibility in determining what proposed innovations should be subject to or exempt from IRB evaluation requires an informed and reflective surgeon and an appropriately educated and empowered oversight committee (see Fig 1).

**Innovative Therapy Thresholds**

The Lasker Forum Report on Ethical Challenges in Biomedical Research and Practice described 3 societal expectations of an oversight process for innovative therapy: the process must protect patients, encourage thoughtful innovation, and expand public confidence and trust. In establishing thresholds for oversight, consideration should be given to the degree to which the procedure departs from usual practices, the adequacy and quality of information used to estimate patient risk, and the likelihood that the treatment will be successful. Other factors to be considered include the context, motivation, and expertise of the institution and proposed provider(s) of the innovative therapy. In some instances, the motive may be entirely patient-centric (ie, for a patient who has exhausted all options of standard therapy and for whom an innovative procedure, offered on compassionate grounds, is the only treatment option). In other situations, the motives may reflect perceived or real conflicts of interest for both the hospital and treating surgeon. Examples include hospitals that are test centers for the surgical device industry or that advertise...
the availability of innovative procedures as a marketing tool on public Web sites and surgeons who receive commercial benefit and/or academic advancement from the development of the procedure. Any conflicts, perceived or real, must be fully disclosed and actively managed by the institutional approval process and again during the process of obtaining patient consent for the procedure.

**Institutional Oversight for Innovative Therapy**

When a practitioner or a hospital wishes to offer a procedure that meets the definition and threshold of “innovative therapy,” an oversight and adjudication process is required that meets the delicate balance of assurance of patient protection, maintenance of public confidence and trust, and the promotion of procedures that are likely to offer “new” benefits to patients in the short- or long-term. (It is assumed that such a process could only be applied in patients whose care needs do not mandate urgent or emergency intervention. Decisions around the use of innovative therapy in time-sensitive clinical situations require a rapid consultative process involving the patient and family, clinical team, experts, and often, a clinical ethicist and is not within the scope of the following discussion.)

An innovative therapy “application” (Fig 2) must include a contemporary literature review, which reports the clinical experience with the proposed procedure or technology in children (if any exists), in adults, or in experimental models if no clinical evidence exists. Where clinical evidence does exist, the review should specify clinical effectiveness outcomes as well as risks and adverse events, especially those that were unexpected. Alternative, currently available therapies and why they might be inadequate for treatment should be reviewed. The application should detail the circumstances of where and by whom the care will be delivered, what the immediate postprocedural surveillance will be, and a follow-up plan. If the expectation is that more than 1 patient will be treated, there must be a commitment to review outcomes after a defined number of procedures. Evidence of the foundational knowledge and skills of the individual or team performing the procedure should be provided, including a description of any preparatory work performed via structured courses, simulation, animal or cadaver laboratory experiments, or any other steps taken to maximize the expertise of the providers and safety of the procedure. If appropriate, consideration should be given to the use of a preceptor or proctor to support the practitioner and team as it progresses along its “learning curve.” Specific outcomes that reflect the expertise of the team (eg, operating times or blood loss) should be monitored with an expectation that unexpected outcomes or adverse events may be justification for the revocation of privileges to perform the procedure.

**FIGURE 1**

A proposed pathway for differentiating innovative therapy from clinical care and research. *Assumes that patient condition allows sufficient time for evaluation by this process. RCT, randomized controlled trial.*
The application process also requires an objective assessment of any real or perceived conflicts of interest that may exist. Although these conflicts need not prevent the approval of the innovative therapy application, they must be addressed directly and candidly with the patient and parents or legal guardian during the consenting process so that all can decide whether the conflict has influence on their decision to proceed with the innovative procedure.

The adjudication and ongoing oversight (after implementation) of an innovative therapy protocol should be the responsibility of a small leadership group that has clinical expertise with the condition being treated or the proposed technology, a clinical leader from another department, and possibly a clinical ethicist, especially if conflicts exist for either the practitioner or the institution.

### The Process of Informed Consent and Shared Decision-Making

The informed-consent process includes a frank and transparent discussion between surgeon and patient (and when the patient is a minor, the family) in which the surgeon describes the proposed treatment as well as therapeutic alternatives while the patient and family demonstrate their understanding of the potential impact of the proposed treatment on clinical and quality-of-life outcomes. The process requires the physician to determine, with clarity, where the proposed intervention resides along the spectrum between clinical care and research. If there is any question that a procedure might best be offered under a research protocol, even if the intent is to treat the patient, the surgeon should seek an IRB opinion. The physician-patient relationship, founded on trust and honesty, underpins the informed-consent process. This process underpins the informed consent process and implies transparency of information about the risks and outcomes of the proposed procedure as well as alternative treatments. When obtaining consent for an innovative procedure, it is appropriate for the surgeon to report his or her personal experience, including case volumes and patient outcomes. In a situation in which there is a paucity of patient outcome data to consider, the physician, patient, and family can be vulnerable to “optimism bias,” which is an unwarranted belief in the effectiveness of new therapies. The surgeon with a passionate commitment to the innovative procedure is especially vulnerable, particularly if sacrifice and perseverance have played substantial roles in procedural development. To avoid optimism bias (or its perception) on the part of the surgeon, consideration should be given to the participation of an objective third party while obtaining consent. Optimism bias in patients...
can be mitigated by imposing a mandatory “cooling off” period after the initial discussion, followed by a second visit at which point a consent can be signed.20

The patient and family may believe that the surgeon’s willingness to offer an innovative procedure is something they must accept, especially if they think that to refuse would disappoint or offend their surgeon and could lead to the withholding of care. There may be a number of associated factors, including a previous physician-patient relationship, contributing to a sense of obligation to participate. The process of informed consent must also be sensitive to a variety of other influential factors including preferred language, educational level, health literacy, and cultural practices, inviting a possible role for nonfamily members (community elders) in the discussion.21 Consideration should also be given to the potential role of a primary care pediatrician or other physician with whom the family has a trusting relationship as a supportive intermediary in the informed-consent discussion.

**Unique Issues of Consent for Innovative Procedures in Children**

When the patient is a child without decision-making capacity, the medical legal system grants parents the authority to provide permission for treatment on their child’s behalf. For many countries and most US states, the “age of majority” is 18 years. Persons below the age of majority are said to be “minors.” There are circumstances in which minors are able to provide their own consent (ie, “emancipated minors,” such as those in the military and those who are living independently or married), and this situation would apply to innovative procedures. There are other minors who have the intelligence, maturity, and insight to understand the nature and consequences of a proposed medical procedure but who are not autonomous, and they can provide assent, meaning that they agree to treatment in circumstances in which they are not legally authorized to give consent. Physicians should always seek to obtain a minor’s assent along with parental consent.

Other conflicts may occur with the introduction of innovative therapy into clinical care. A potential conflict related to innovative therapy might be a procedure offered to a minor on compassionate grounds, when no good standard alternatives exist, and when potential benefits and risks to the child are not well known, limiting the patient’s and family’s ability to provide informed consent to the procedure. For example, disagreement between parents and their minor child may arise with respect to the initiation or withholding of potentially life-sustaining innovative therapy, when there is the potential for dissent between the parents and child.

Options for resolution of conflict between a consenting parent and a dissenting minor include additional consultation (“second opinions”), family counseling, multidisciplinary case conferences that include the primary care physician and those individuals who are trusted by and know the patient and family well, and consultation with a clinical ethicist.

**Facilitating the Inclusion and Participation of Minority Children in Innovative Therapy**

Assessing treatment efficacy across a population is determined by a number of factors including patient race and sex. For the results of clinical trials to be generalizable, racial and sex enrollment bias should be minimized. For this reason, the inclusion of women and minorities in clinical research was mandated in 1995.22 A commonly held belief that patients from minority communities are distrustful of clinical research has some basis in adult studies,23 although there is little evidence of this in the pediatric population as shown by minority racial participation in children’s cancer trials.24 If a new surgical intervention requires evaluation, either as clinical research or under an innovative therapy protocol, it is essential that there be no barriers to the intervention being offered to all children, which means having translated written materials and consents as well as certified medical interpreters (assuming no physicians) available to explain the procedure and treatment alternatives. There should also be flexibility in the consenting process that would allow the participation of others (eg, a relative or community elder), in addition to the parents, if desired by the family, so as to optimize the accuracy of information transfer, transparency, and confidence of the family in the consenting process. Just as it is important to ensure unrestricted access to innovative procedures by minority or disadvantaged populations, it is equally important to ensure that these populations are not sought out for the clinical evaluation of an innovative procedure.

**Innovation and Value**

In health care, value has been defined as health outcomes relative to the costs of delivering the outcomes.25 Although this concept may seem to be obvious, the value proposition of any innovative therapy can be difficult to predict, at least initially, because neither the health outcomes nor health system costs are fully known. New surgical device technology, especially that which is “disruptive” to the existing markets, is frequently associated with increased costs, at least initially. This situation is not necessarily bad as long as the new technologies result in clear outcome improvements; value does not necessarily mean cost reduction. However, one can
usually assume that if an innovation proves effective, costs will come down as more vendors seek to be competitive within that technology space. Although the initial product cost for innovative technologies may be easy to quantify, the opportunity costs of additional operating time associated with new surgical devices as well as additional infrastructure, hospitalization, and support costs may be difficult to capture. On the numerator side, surgical outcomes have also been challenging to quantify and prioritize. Beyond measureable outcomes, such as mortality, length of stay, complication rates, and possibly postoperative pain, our ability to capture outcomes that matter most to patients (so-called patient-reported outcome and patient-reported experience measures) is limited and lacks surgical disease and procedure specificity. In surgery, this value equation is further complicated by the fact that its elements are dynamic. Improved outcomes associated with progression along the learning curve as well as changes in the cost of technology driven by competition and changes in market share alter the equation over time. Other opportunity costs that may be overlooked with the implementation of innovative surgical care are the allocation of resources to create surgical team expertise through training and dedicated nursing teams, the need for additional operating room time, and incremental costs associated with disposable equipment. In addition, longer operating room times associated with the adoption of innovative technology have a hidden opportunity cost, which is the lost revenue from procedures that were not performed in that time.

Any oversight committee charged with the responsibility of approving the use of innovative therapy must navigate a challenging path that ensures patient safety and informed choice but avoids a “stifling” bureaucracy that could prohibit or profoundly delay the implementation of an otherwise promising treatment with a high likelihood of patient benefit and the potential for future significant cost savings.

SUMMARY AND RECOMMENDATIONS

1. Innovation in children’s surgery should be encouraged and driven primarily by contemporary gaps in care and opportunities for improvement identified by both practitioners and patients.

2. The determination of where a proposed innovative surgical procedure lies on the continuum between clinical practice and clinical research should consider both the degree of departure from usual practices, as well as the evidence of effectiveness and what is known (or unknown) about the risks of the procedure.

3. Although IRBs are the preferred mechanism of oversight when the primary goal of an innovative therapy proposal is the creation of generalizable knowledge (eg, clinical trial), alternative oversight mechanisms are usually required when the primary intent of an innovative therapy is the treatment of a patient with limited conventional therapeutic options.

4. All hospitals providing care to children should use an innovative therapy protocol/process that allows rigorous adjudication, implementation, and postimplementation surveillance of innovative procedures in children. This process should offer the assurance of patient protection and maintenance of public confidence and trust and should promote procedures that are likely to offer maximal benefit from the patient’s and family’s perspective.

5. The process of informed consent for innovative surgical procedures in children should include, in addition to the usual consent for surgery, a discussion of how the procedure differs from conventional therapy and the fact that all possible outcomes may not yet be known. The process should include full disclosure of any real or perceived conflicts of interest and should consider the involvement of an objective third party and a mandatory “cooling off” period before the granting of consent. Every effort should be made to obtain assent from an age-appropriate child.

6. Innovative surgical therapy for children should be made available to all children, regardless of race or socioeconomic status. Methods of offering and obtaining informed consent must be sensitive to the unique needs of families with respect to language, culture, and health literacy.

INTERNET RESOURCES RELATED TO INNOVATIVE THERAPY IN CHILDREN


US Food and Drug Administration’s Pediatric Device Consortia program. Available at: http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/PediatricDeviceConsortiaGrantsProgram/

Wanted: Specially Designed Tools for Pediatric Surgery. Available at: http://www.npr.org/sections/health-shots/2012/02/20/147037665/wanted-specially-designed-tools-for-pediatric-surgery

LEAD AUTHORS

Erik D. Skarsgard, MD, FAAP
Aviva L. Katz, MD, FAAP
Mary E. Fallat, MD, FAAP
REFERENCES


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