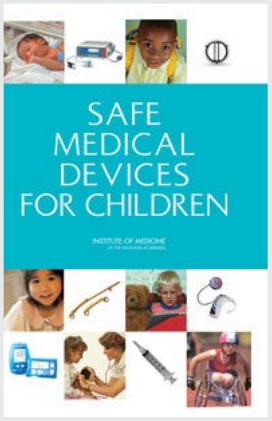

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SAFE MEDICAL DEVICES FOR CHILDREN

Committee on Postmarket Surveillance of Pediatric Medical Devices

Board on Health Sciences Policy

Marilyn J. Field and Hugh Tilson, *Editors*

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The serpent has been a symbol of long life, healing, and knowledge among almost all cultures and religions since the beginning of recorded history. The serpent adopted as a logotype by the Institute of Medicine is a relief carving from ancient Greece, now held by the Staatliche Museen in Berlin.

Front Cover Photographs:
Top row, second from left: CO2SMO® Capnograph/Pulse Oximeter (Used with permission of Respironics, Inc., Murrysville, PA).
Top row, fourth from left: SJM Regent® Valve (Courtesy of St. Jude Medical, Inc.).
Second row, second from left: Vertical Expandable Prosthetic Titanium Rib (VEPTR) (Courtesy of Robert M. Campbell, M.D., Thoracic Institute, CHRISTUS Santa Rosa Children's Hospital).
Second row, fourth from left: Auria BTE Processor (Courtesy of Advanced Bionics Corporation).
Third row, first from left: Medtronic Paradigm® 515 insulin pump and Paradigm Link™ monitor (Reproduced with permission of Medtronic, Inc.).
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Once the optimal time to begin a pivotal clinical trial is established, decisions concerning which venue and which clinicians to engage in testing a particular device can have a major effect on how the results of the trial will be interpreted and whether the device achieves broader usage. In contrast to pharmaceuticals, the efficacy of a surgically implanted device can be linked to the skill of the implanting surgeon. If there is substantial variation in skill among trial investigators, the results of the trial may be difficult to interpret. A positive average outcome for the experimental therapy may only be positive because of a few exceptionally well-skilled clinical sites, and a negative average outcome may only be negative because of a few, poorly skilled clinical sites. Clinical researchers must be on the guard for such outcomes. Trials typically offer a separate randomization scheme for each clinical site so that each site is balanced with respect to the number of experimental and control patients that they treat. Moreover, examining the effect of study site on the primary outcome is a routinely performed analytical step. One strategy to assure uniformity of skill is to engage in a pilot trial or run-in period, which will not be counted in the final analysis. Another is to limit participation to individuals that have a particular skill level. Conducting a trial in a highly specialized center with unique surgical expertise may result in a successful trial, but may not be generalizable to widespread usage or provide useful information on the economic value of using the device in less specialized centers.

Pediatric patients are considered a vulnerable population in the context of conducting clinical research. Research that presents more than a minimal risk without the chance of direct benefit to the child is unlikely to be approved by an Institutional Review Board (IRB). Those trials that are approved involve special considerations regarding the informed consent process. Only the parent or legal guardian has legal standing for signing a statement of informed consent for a minor (the age cut-off varies by state). However, older children, who have the capacity to understand the activities involved in trial participation, need to give their assent for the participation.

Blinding, an important technique for controlling observational bias when evaluating the safety and efficacy of a new clinical intervention, is an issue in invasive or implantable device trials. Obviously, it is impossible for the clinician that implants a device to be blinded. Patient blinding is usually not possible when the comparative therapy is not a device. Thus, randomization is more of a problem in device trials because of the lack of blinding. This is true in particular when there is a life-threatening illness. Here both patient (their family) and physician will have expectations that the device is their best hope and would be devastated to learn, up front, that they would not receive the preferred therapy. This could deter some patients and physicians from entering into a device trial, while others might enroll but seek treatment outside the protocol if they didn't receive the therapy they wanted.

This might lead to a loss-to-follow-up or out-of-protocol crossover, which could ruin a small-scale trial. The ethical dilemma here is heightened when there are no alternative therapies and assignment to a control arm means essentially no therapy (Moskowitz et al., 1997).

Measuring survival in trials that compare devices and medical therapies poses methodological challenges. When device therapy involves a high up-front operative risk, but subsequently a reduced mortality compared to the control group, the survival curves are likely to cross. Analyzing the differences between such curves depends on the analytical method chosen and the time frame of the analysis. Most analytical methods (e.g., log-rank, Wilcoxon test) average risk over the follow-up period. So, extending or reducing the follow-up time has the potential to reverse the ordering of relative efficacy because less or more weight, respectively, will be given to the mortality in the peri-operative period (Rose et al., 1999).

Measuring the effects of treatment on children's quality of life is a more complex task than for adults, largely because children are developing (Rosenbaum and Saigal, 1996). Any assessment of functional status must be performed in a developmental context. Key aspects of quality of life (such as physical, emotional, and social function) develop rapidly as the child ages, which means that a group of questionnaires must be developed that are specific for an age group. Similarly, age-adjusted normative values are needed to put the measured values in the context of the general population. For younger children at an earlier stage of intellectual development, investigators must rely on parents or caretakers to act as proxies for direct patient-based responses. Despite these challenges, there has been considerable progress in the field of quality of life assessment for children, with new survey instruments, both generic and disease-specific, being developed and validated in a range of pediatric conditions (Drotar, 1998; Eiser and Morse, 2001; Koot and Wallander, 2001).

Assessment of the economic value of devices is challenging in pediatric populations for many of the same reasons that it is difficult to assess clinical outcomes. The small patient populations that frequently result in single-arm studies or registries hamper not only the identification of treatment effects, but also leave the assessment of cost-effectiveness without a comparator. The short-term nature of many randomized trials makes it difficult to accurately assess the long-term economic impact of treating a particular patient population for the individual payer. Economic analyses typically use outcomes such as costs per life year saved or quality-adjusted life-year (QALY) saved, which require survival projections. In the case of children with long life expectancies, these projections are more difficult to make and, consequently, involve greater uncertainty. Moreover, the tendency to conduct pediatric device trials in highly specialized treatment centers makes it difficult to infer the economic value of the use of devices in less special-

ized centers. In recent years, there has been an increase in economic evaluations for pediatric populations. Ungar and Santos (2003) created a pediatric economic database and documented a 7-fold increase in publications between 1980 to 1984 and 1995 to 1999. Currently, the database contains over 1,000 citations of full economic evaluations from January 1980 to the end of December 2003. However, searching the database for device-related economic evaluations, we found only 30 citations analyzing 11 different device categories (e.g., cochlear implants, amplatzer catherization techniques for occlusion of atrial septal defects, and laparoscopic spelenectomy). Most of these evaluations were conducted in the last 5 years, indicating an emerging trend.

In short, rigorous trials can provide important evidence about the efficacy, safety and—more recently—the economic impact of new pediatric devices. Regulatory decisions then have to combine this empirical evidence with qualitative judgments about the acceptability of the trade offs between benefits and risks associated with new technologies, and payers have to combine the empirical evidence with qualitative judgments about the acceptability of the trade-offs between benefits and costs. Such trade-offs depend upon the disease context and available alternatives, the preferences for the outcomes at stake, and the amount of uncertainty in achieving them. Given that premarket trials are based on a sampling process, there will always be uncertainties. Attempting to eradicate uncertainty is impossible, and attempts to bring the level of uncertainty down to minute levels would be costly in terms of the time and expense of the premarket development process, as well as the indirect expense of holding off a promising therapy from patients. Diminishing these uncertainties will require widespread clinical use and analyzing the outcomes in the postmarket setting.

Adoption of a New Device, Feedback, and Continued Innovation

The adoption of a new device in widespread clinical practice does not signal the end of the development process. In fact, widespread use is typically a prerequisite for garnering insights about the technology that provide important feedback to the R&D sector, either in industry or academia, about necessary improvements to optimize ease of use and the associated outcomes. These second-generation devices then re-enter the cycle of preclinical and clinical evaluative studies.

Ongoing innovation, however, does not only take place in R&D laboratories, but also in clinical practice itself. A common phenomenon is that, with further experience, improved strategies of managing patients with a device may emerge, including changes in the operative intervention, postoperative management, and outpatient care. In addition, the selection of

patients tends to change and expand. An interesting example can be found in laparoscopic surgery. Consider the transition from open surgical procedures to minimally invasive surgical approaches. These laparoscopic procedures tend to minimize post-operative pain and recovery time, and may reduce the treatment cost per patient. As a result, the target population for these procedures has expanded. Often this includes less sick patients for whom the risks of the procedure are now acceptable or sicker patients who initially were too risky to be candidates. This potential to expand the target population suggests that elasticity of demand for medical services is greater than commonly supposed.

In addition, totally new indications for use may emerge from the application and mastery of seemingly routine practices. Most medical devices achieve new indications by transfer from one organ system to another, although these transfers often require design modifications. The first endoscopes, for example, were used for cystoscopy early in this century. In the 1960s, after the development and introduction of fiber-optics, gastrointestinal endoscopy and gynecological laparoscopy became well established. A further extension of endoscopy depended on the eventual joining of television cameras to the scope, which facilitated their use in procedures such as arthroscopy. Widespread use is often a precondition for identification of these new uses, and clinical practice itself is a central source of medical innovation. "Learning by doing" in clinical practice, which may suggest modifications in the technology and the design of confirmatory trials, is widespread and confers broad health and economic benefits. A study of the top 20 blockbuster drugs from 1993 found that secondary indications exceeded 40 percent of revenues, and that a similar pattern held for medical devices (Gelijns et al., 1998)

Postmarket Evaluation

There are various reasons, as suggested above, why it is important to collect outcomes data in the postmarket setting. Premarket trials have limited time frames and seldom measure long-term effectiveness or safety. In pediatric clinical trials, the long life expectancy of children offers ample opportunity for late consequences of a disease, or treatment, to develop, which may be unknown at the time of treatment. The delayed consequences of radiation treatment of the face for teenage acne, for example, were only seen decades after treatment as an increased incidence of thyroid cancer. Trials also intentionally limit patient heterogeneity and, therefore, may not be generalizable to all potential recipients, who will receive the device in the postmarket setting. Moreover, premarket trials are often conducted in specialized centers, and as the device disseminates to other participants, the outcome parameters may change.

The iterative nature of medical device development argues for continued monitoring of devices as they are used in general clinical practice. There are various ways in which postmarket data can be collected. Mandatory and voluntary reporting of device-related deaths and serious adverse events to the FDA by manufacturers and clinicians has been plagued by underreporting. As part of the voluntary reporting system, the FDA has been implementing the MedSun system since 2002, an Internet-based pilot reporting system, comprised of over 180 hospitals and nursing homes.

The FDA could also mandate more postmarket studies or registries as part of the PMA approval. Clinical trials in the postmarket setting may differ substantially from premarket studies in their target populations, endpoints, and comparison groups. While FDA-related trials in the premarket setting may utilize a placebo control group (although not often with devices), postmarket studies are more concerned with comparisons between alternative treatment options. Postmarket studies are more apt to use a general practice setting than "centers of excellence" and to expand the target population beyond those seen in premarket studies. Moreover, they are more likely to include a broader range of outcomes, including functional status, quality of life, and economic endpoints facilitating much more accurate and meaningful estimates of the cost-effectiveness of new treatment options.

Specialty societies or regional authorities might also independently initiate such registries. For example, consider ECMO or extracorporeal life support (ECLS), which is a modified form of cardiopulmonary bypass, used in children and adults (Zapol et al., 1979). As the use of ECMO gained in popularity in 1984, the Neonatal ECMO Registry was established and began collecting data on in-hospital outcomes from clinical centers. To date, ECLS has been employed in more than 26,000 neonatal and pediatric patients with an overall survival rate of 68 percent (Lequier, 2004). In the United Kingdom, clinical trials are now being conducted to assess the long-term outcomes of ECMO. Another case in point is the New York State Cardiac Advisory Committee, which required all hospitals in New York State to collect data on the in-hospital outcomes for pediatric patients undergoing surgery to correct congenital cardiac defects. The risk-adjusted outcome rates for the specific hospitals can be used in quality improvement programs. Generally speaking, either hospitals or the device manufacturers conduct these postmarket observational studies. A more recent model of postmarket data collection involves LVADs. As a condition of marketing and reimbursement approval of the HeartMate™ LVAD for destination therapy (long-term implantation) in patients with advanced heart failure, the manufacturer must collect long-term data on patient outcomes and device performance for all patients receiving the implant. Three major government agencies (FDA, CMS, and NIH) have put for-

ward funds to support the registry, which would be coordinated by an independent organization. The participating hospitals would provide in-kind support for data collection efforts, while industrial firms would provide additional financial support. The expectation is that industrial firms would assume the responsibility for the registry over time. Models like this might provide interesting formats for the pediatric device world where private sector funds are limited.

CONCLUDING OBSERVATIONS

Incentives for innovation in the area of pediatric devices are far less compelling than for the adult population. Generally speaking, this area is characterized by small markets, limited reimbursement, and formidable challenges to conducting premarket trials. The perception is that these obstacles have resulted in unmet needs for diagnosing and treating diseases in children. Many diseases could benefit from improved or novel devices (such as pediatric LVADs for cardiomyopathies). Although, in some areas, the demand has been partially met by clinicians modifying adult devices for use in children (such as the use of adult biliary stents for pediatric intravascular placement); this process is affected by the risk of little oversight of good manufacturing practices. Federal agencies have called for more data collection to better assess these unmet needs.

Although the extent of the problem is not defined in detail, expert opinion indicates that a strong case can be made for stimulating clinical innovation (including device innovation) in pediatrics (FDA, 2004b; see also AAP et al., 2004). Such innovation could lessen the substantial emotional and economic toll imposed by childhood diseases. However, as this paper argues, there is an equally strong case to be made for a more rigorous knowledge base about the effectiveness, safety, and economic impact of device modalities for children. Premarket clinical trials are limited in their ability to provide insights about long-term effectiveness and safety, resulting in uncertainty about the ultimate value of these devices. Moreover, this uncertainty is exacerbated by the fact that devices keep evolving long after they have moved out of the clinical development phase into widespread clinical practice itself. Observations by users about the limitations of devices are fed back into the R&D process and may lead to subsequent modifications. In addition, physicians modify the clinical management strategies for their device patients (e.g., implantation techniques, infection prevention techniques, or means to diminish bleeding), and change the selection criteria for patients eligible for device therapies. This evolution, which is largely based on tacit know-how and usually not subjected to formal experimental testing, further heightens the uncertainty level about the clini-

cal and economic impact of devices, and, hence, our understanding about best practices in caring for patients.

Yet, there is a tension between stimulating innovation and increasing the requirements for collecting more data on the clinical and economic impact of device therapies, which is exacerbated by the small size of many of the markets and affected patient populations. Attempting to eradicate all clinical uncertainty in the premarket phase is impossible, and attempts to bring the level of uncertainty down to minute levels would be costly in terms of the time and expense of the premarket development process, not to mention the indirect expense of holding off a promising therapy from patients. Diminishing these uncertainties requires widespread clinical use and ongoing outcomes assessment in the postmarket setting. However, even if we emphasize postmarket data collection, we need ensure that this in itself does not impose an additional disincentive to pediatric device innovation.

What then are some of the options for achieving this? Facilitating the process of premarket and postmarket trials requires solutions that lie within the analytical, institutional and financial realms. First of all there are various ways of decreasing the sample size for premarket clinical trials. This is important because, in general, pediatric disease populations are small enough that enrollment times would be lengthy and threaten the usefulness and validity of the results of the trial as well as drive up the related costs. Techniques such as Bayesian analysis, which utilize prior probabilities in the hypothesis testing, relaxing the tolerance to random variation error (i.e., utilizing more relaxed confidence intervals), or utilizing non-concurrent control groups and objective performance criteria, each can reduce the required sample size compared to a classic randomized controlled trial. Another consideration is to eliminate requirements for extensive premarket studies in children when the device in question has been used widely in adults, the pathophysiology of the disease is similar in adults and children, and the adaptation of the devices requires no major technological changes (FDA, 2004b).

Another important set of initiatives can be found in the institutional realm. We need to strengthen the institutional infrastructure for conducting clinical trials for devices in pediatrics by creating networks of pediatric hospitals. A case in point is childhood cancer, which constitutes a fairly small population. Nearly 95 percent of children with cancer under age 15 are treated at institutions that are affiliated with the Children's Oncology Group, resulting in more than 70 percent of cancer patients in this age group being enrolled in one or more clinical trial (Tejeda et al., 1996; Bleyer et al., 1997). Although the group focuses on evaluation of multi-modal cancer therapy (i.e., effective use of combinations of surgery, radiation, and chemotherapy), this network, with appropriate public or private funding,

may be used for evaluation of surgical, radiological, and drug delivery devices. These U.S. hospital networks should also become involved in data collection in the postmarket setting, which requires better integration of data collection for these studies with the data collection systems used in everyday practice of medicine. These institutions could be induced to participate through better reimbursement rates for the care they provide or through direct subsidy for data collection efforts by research agencies. The NIH, for example, sponsors the pediatric heart disease clinical research network to study new interventions for congenital heart disease.

This brings us to the financial realm. There is an increased need for public–private partnerships for funding premarket trials of innovative pediatric devices (as per the philosophy of the NIH Roadmap) and postmarket studies. The products of this research are subject to the classic public good argument, where health benefits would accrue to the public-at-large, but investors would be unable to derive a sufficient return on their investment. Alternatively, one could also argue for increasing the financial incentives to the private sector, which would be able to raise private funds for developing and evaluating novel pediatric devices. Among suggested incentives are decreased or capped liability or better reimbursement for pediatric device therapies.

The need to obtain better knowledge about the clinical and economic impact of devices, especially in the postmarket setting is a general one. The pediatric case, however, offers unique challenges in that the incentives to innovate are weak as a result of small populations, which also complicates the clinical trial process. Therefore, the case is especially strong for the creation of novel partnerships between the public and private world that would experiment with new analytical, institutional, and economic models.

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