Published in final edited form as:

ASAIO J. 2009 ; 55(1): 10–12. doi:10.1097/MAT.0b013e318198e13d.

Pediatric Circulatory Support Contractors' Meeting: Report of the Clinical Trials Working Group

Steven A. Webber, MBChB, Peter D. Wearden, MD, PhD, Elizabeth D. Blume, MD, Christopher Almond, MD, Kathryn O'Callaghan, BS, Eric Chen, MS, Gail Pearson, MD, ScD, and Timothy Baldwin, PhD

University of Pittsburgh School of Medicine and Children's Hospital of Pittsburgh of UPMC (SAW, PDW); Children's Hospital Boston and Harvard Medical School (EDB, CSA); FDA Center for Devices and Radiological Health, Office of Device Evaluation, Division of Cardiovascular Devices (KO, EC); Heart Development and Structural Disease Branch, Division of Cardiovascular Diseases, National Heart Lung and Blood Institute, National Institutes of Health (GP); Advanced Technologies and Surgery Branch, Division of Cardiovascular Diseases, National Heart Lung and Blood Institute, National Institutes of Health (TB)

BACKGROUND

A clinical trials working group of the Pediatric Circulatory Support Contractors met at the annual Contractors' Meeting on February 28, 2008. The overall goal of the workshop was to make recommendations for the development of Investigational Device Exemption (IDE) clinical trials of mechanical circulatory support in neonates, infants and young children. While the recommendations were primarily developed for trials involving emerging devices designed specifically for use in the pediatric population, they are also expected to be applicable to pediatric usage of existing adult technologies. The workshop was not designed for discussion of specific trials of individual devices. The meeting was attended by representatives of industry, academic medical centers, the U.S. Food and Drug Administration (FDA), and the National Heart Lung and Blood Institute (NHLBI) of the National Institutes of Health. A brief summary of the main topics of discussion follows, along with specific recommendations where appropriate. It is noted that most discussion revolved around cardiac support without the need for oxygenation, though it was acknowledged that the need for both cardiac and pulmonary support is quite common in the pediatric age group.

A brief executive summary at the end of this report highlights the priority action items for the field to move forward. This report was compiled by the working group listed in the

Address for Correspondence: Steven A. Webber, M.B.Ch.B., MRCP, Department of Pediatrics, Vanderbilt University School of Medicine, 2200 Children's Way, Suite 2404, Nashville, TN 37262-9900, Tel: 615-322-3377; FAX: 615-936-3330, steve.a.webber@Vanderbilt.Edu.

Note: It is recognized that there are other forms of circulatory support than VADs, and that oxygenation is a frequent requirement during circulatory failure in children. However, most of the attendees have focused their efforts on the development of pediatric circulatory support with VADs. Thus, most discussion focused on this form of support. This does not negate the importance of study of other forms of circulatory support in children, nor does it imply that these devices could not be included in the above-mentioned network design.

document, and does not necessarily reflect the opinions or recommendations of any specific individual, group, or any agency/institution.

EPIDEMIOLOGY OF DECOMPENSATED HEART FAILURE IN CHILDREN

The number of children requiring mechanical circulatory support, primarily for cardiac reasons, remains small. However, the actual number of children who might benefit from improved technology is unknown. The limited types of support currently available for children, the absence of “off the shelf” devices, and the lack of experience and training in many centers have limited the demand. Potential usage may be significantly higher than current demand. For example, in most centers, post-cardiotomy heart failure is managed with extracorporeal membrane oxygenation (ECMO) with the expectation of short-term (7–14 days) support. This algorithm might be changed if alternative devices were readily available. The number of children that might benefit from support with ventricular assist devices (VADs) was felt to be within the range of 100–500 per year in the United States. The working group felt that research and development should focus on the population that cannot be readily supported with currently approved VADs (i.e., ²). It was also noted that the population requiring VAD support is far more heterogeneous than for adults. This heterogeneity encompasses age, body size, diagnosis, indications for support and long-term goals of support (bridge to recovery, bridge to transplant, bridge to decision etc). This heterogeneity emphasizes the need for a range of device types and sizes to be studied within trials under IDE applications. The limited population available for such studies was recognized.

OVERALL CLINICAL TRIAL DESIGN

While some forms of support may target specific populations with unique characteristics, the majority of VADs currently under development could have overall study designs which are broadly comparable to each other. Whenever possible, standardized study designs with common safety and effectiveness end-points (primary and secondary), standardized definitions of adverse events (AEs), and common data collection instruments (e.g., case report forms) should be used, which will allow for comparison of devices, especially safety profiles. Well-defined anticoagulation/anti-platelet protocols and mechanistic studies of thrombosis and bleeding should also be incorporated into all pediatric VAD study designs. It is recognized that inclusion and exclusion criteria are likely to vary for different devices, but overall, future studies are likely to have more common components than differences. This could lead to a consortium model of funding, where several device trials are managed within a consortium arrangement by a funding agency such as NHLBI. Cooperative agreements and contracts have been very successful in other settings in which multiple trials are performed in parallel within multi-center consortia (e.g., Pediatric Heart Network by NHLBI; Clinical Trials in Organ Transplantation by NIAID). Within such a consortium, it might be possible to define ‘control populations’ that could serve as comparators for more than one device study. Potential ‘control’ groups suggested for matching include: (1) optimized medical management populations treated without VAD support, (2) ECMO patients, or (3) potential objective performance criteria (OPCs) based on literature-reported outcomes with an approved device. Although ideal scientifically, and worthy of further discussion, it was

generally felt that randomized controlled trials would unlikely be achieved in the pre-approval phase of device development in children. The optimal sample size for non-randomized trials is not defined. It was felt that a minimum of 20 patients would seem reasonable for all IDE studies but that the exact number will depend on the study design. It was acknowledged that new devices never used in humans would warrant extremely close scrutiny and that preliminary device evaluation should probably be performed after a very limited initial experience (for example after the first 5 implants).

PATIENT POPULATIONS AND EXCLUSION / INCLUSION CRITERIA

A major focus of discussion was the marked heterogeneity of pediatric candidates for circulatory support. Some recommended that devices should first be tested within a more homogeneous population such as those with dilated cardiomyopathy not yet on mechanical support. This would make it easier to evaluate the performance and safety of new devices in the pediatric population. This ideal study, however, would be limited by the small patient numbers. Initial usage in high risk populations (e.g., congenital heart disease with single ventricle physiology, post-cardiotomy pump failure, conversion from ECMO) might lead to poor clinical results for devices that may have favorable performance in lower risk patient groups. In these clinical settings, it would be critical to have clinically similar comparison groups. Conversely, it was emphasized that it is important to study devices for those indications for which they will likely be used after FDA approval. It would be hard to generalize results if only the lowest risk populations were studied in the IDE trials. While complete consensus was not reached, one recommendation was to study a relatively homogeneous population (e.g. dilated cardiomyopathy, or congenital heart disease with two ventricle physiology and no intracardiac shunting) for an initial IDE trial of a specific device. Higher-risk patients not fulfilling study entry criteria could be enrolled within a parallel registry (i.e., separate cohort under the IDE) with comparable data collection and study end-points but would not be part of the main clinical cohort of the IDE study.

It was also noted that we must be cautious about excluding pediatric patients with advanced end-organ dysfunction. Pediatric patients with acute organ failure are known to recover quickly when adequate circulation is established. Indeed, acute organ failure is generally considered an indication for immediate support in children. By contrast, many adults experience acute-on-chronic organ dysfunction at times of low cardiac output state and recovery may be less predictable. Finally, it was noted that there must be consensus definitions of potential inclusion criteria such as “decompensated heart failure” and “cardiogenic shock” in pediatric populations. Ideally, these should not be study-specific but should be applicable to all studies.

OUTCOME MEASURES AND DATA COLLECTION MECHANISMS

The major outcome measures will be similar to those of adult VAD studies, though some will require modification for pediatric populations. Survival (to recovery or transplantation) and prevalence of serious AEs will be key outcomes, as with adult devices. An additional end-point of clinical relevance is duration of support for which eligibility for transplantation is maintained. The paradox of bleeding vs. non-hemorrhagic stroke and other thrombotic/

embolic complications remains the single greatest challenge for pediatric device development and must be studied in detail. Reversibility of end-organ dysfunction from immediately pre-implant to defined points during follow-up must be documented. For end-organ function, normal ranges must be defined for patients of various age groups or body sizes and these definitions should be used across all studies. Another important challenge will be the development of criteria for weaning from support in pediatric patients. At present, minimal attention and research has focused on this topic.

Definitions of AEs must be standardized. To a large extent this has already been achieved by the pediatric subcommittee of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS). Age appropriate stroke scales and neuro-developmental and quality of life evaluations should be incorporated into all studies and uniformly applied to allow for broad comparisons between studies. It is recognized that the quality of life evaluations will need to be modified from adult studies and must take into account that most, if not all, pediatric recipients of novel devices will remain hospitalized throughout the period of mechanical support (at least in the pre-approval phase) and many will not leave the intensive care unit. There was strong support for the use of a modified version of INTERMACS for all data collection for pediatric devices (whether as part of IDE studies, emergency or 'compassionate' usage, or during the post-approval period). Modification will be required to allow for pre-approval use (IDE studies and emergency/-compassionate usage) and during post-approval follow-up. This would allow for uniform data collection within the framework of consensus definitions. This would include the possibility of extension of the database for the inclusion of medical management (without device) or ECMO support to be used as comparator groups for the evaluation of new devices. Limited supplemental data collection for device-specific clinical trials could be added for each device trial as required. There was also strong agreement that centers should not be expected to perform duplicate data collection and submission to different agencies.

SUMMARY OF CONCLUSIONS AND RECOMMENDATIONS

Based on the broad discussions of the Clinical Working Group, the following conclusions and recommendations were developed. (1) Pediatric patients requiring mechanical circulatory support represent a highly heterogeneous population and this argues in favor of evaluation of multiple devices. (2) Randomized controlled clinical trials are unlikely to be achieved for investigational devices. (3) Comparator groups should be defined, utilized, and shared among studies whenever feasible. (4) Adult devices modified for pediatric use require studies in pediatric patients prior to approval through any regulatory pathway. (5) All studies should use uniform pediatric appropriate definitions. (6) IDE studies should use as homogeneous populations as possible and these should reflect the common populations to be supported during commercialization. (7) More challenging (and heterogeneous) populations can be studied in parallel with the primary cohort of IDE studies with comparable data collection, using a prospective registry design. (8) A consortium approach is suggested for pre- and post-approval clinical studies. This would comprise a network of centers that would perform studies within the framework of a collaborative agreement coordinated through the funding agency (the most obvious candidate being NHLBI). (9) INTERMACS represents the most advanced tool for data collection, and has already been

modified for pediatric usage. It is recommended that funding be sought to modify INTERMACS to serve as the main repository for all pediatric VAD studies, including IDE studies, data analysis of emergency and “compassionate” usage (for patients outside of IDE primary cohort) and post-approval studies. Both short and long-term device usage should be studied within this mechanism. (10) Post-approval studies are essential for VADs designed for pediatric use given the small number of patients that will be enrolled in pre-market IDE clinical studies. The objective of these studies would be to evaluate device performance and potential device-related problems in a broader population using pre-defined AEs over an extended period of time, after pre-market establishment of reasonable safety and effectiveness or probable benefit.

Acknowledgments

This work was supported in part by the National Institutes of Health under award number: T32HL007572. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.