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The Neurodevelopmental Consequences of Congenital Heart Disease

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Children's National Heart Institute Cardiac Neurodevelopmental Outcome Program

http://bit.ly/CANDOatChildrensNational

Background

Children with complex Congenital Heart Defects (cCHD) are now surviving neonatal and infant surgery with a frequency thought to be impossible only a generation ago. While advances in Medicine and Surgery have allowed the ability to "mend" children born with CHD, the increasing number of survivors has created a growing population of children in our primary and secondary school systems, and young adults entering the job force.

In the United States alone, over 35,000 infants are born each year with CHD, and more than a third of these infants have cCHD, and will undergo "palliative" or "corrective" surgical interventions in the first year of life. It is estimated that there are more than one million adults now living in the USA with a variety of CHDs, which includes over 150,000 adults living with cCHD. Due to improved survival rates in the past two decades, there are larger numbers of school-age children with increasingly complex forms of CHD. As survival rates have increased, additional attention has been directed toward understanding and treating the long-term challenges for these children and young adults, including behavioral problems, academic performance and mood disorders, all of which combine to affect health-related quality of life.

The "Neurodevelopmental Phenotype" in cCHD (see Table)

As a group, children and young adults with cCHD have a higher likelihood of academic, behavioral, social-emotional and motor coordination problems compared to children without CHD. While not all children with cCHD have these difficulties, the percentage of children with these challenges is significantly higher than in the general population. These problems are more prevalent in children with cCHD compared to less severe forms of CHD that do not require surgery, can be treated during catheterization, or do not require surgery until later childhood (see Figure).

Infancy

In infancy, problems that are more prevalent include feeding difficulties (perhaps in half of all children requiring heart surgery as neonates) and delays in reaching some important motor milestones such as rolling over, crawling or walking – opportunities for them to explore the environment. Although most neonates achieve full feedings by mouth shortly after discharge from the hospital, many require supplemental tube feedings into later infancy and beyond. While delays in motor

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Table*

Neurological, Developmental and Psychosocial Challenges Which Occur with Increased Frequency in Children, Adolescents and Young Adults Born with Critical Congenital Heart Disease

- Stroke
- Seizures
- Abnormal brain morphology and functional connectivity (MRI)
- Abnormal brain growth, cerebral atrophy (CT, MRI)
- CNS hemosiderin deposition (MRI)
- Oral-motor dysfunction
- Poor head control
- Delayed gross and fine motor milestones
- Apraxia of speech
- Clumsiness
- Problems with visual-spatial-motor integration
- Inattention and hyperactivity
- Cognitive impairment
- Impaired memory
- Difficulties with executive function
- Autism spectrum disorders
- Social awkwardness/Impaired social cognition
- Anxiety
- Depression
- Schizophrenia (associated with DiGeorge Syndrome)

Legend: CNS= Central Nervous System; CT=Computerized Tomography; MRI=Magnetic Resonance Imaging

**Modified (with permission) from Wernovsky G and Licht DJ: Neurodevelopmental Outcomes in Children With Congenital Heart Disease-What Can We Impact? Pediatric Critical Care Medicine 2016;17:S232-42.*

skills are extremely common, most of the infant's milestones are delayed by only a few months or so. Following heart surgery in the neonate and infant, many heart centers now perform speech, occupational and physical therapy evaluations and treatment, as well as long-term follow-up – as recommended by the American Heart Association and American Academy of Pediatrics.

Preschool

In preschool, there is a growing recognition of delays in certain elements of speech and language. To greatly oversimplify, speech and language can be broken down into two components: receptive language (the child hears and understands words), and expressive language (using words and sentences to communicate effectively). In many children with cCHD, receptive language is normal (e.g., if you say "point to the apple", the child will point to the apple). In contrast, children may have trouble with articulation (or coordinating the oral movement needed for forming words correctly), and with more complex expressive language. For example, a child may have trouble finding the right words (e.g., when you point to an apple and say, "what is that?", even though the child knows it's an apple), or as they get older, they may have trouble organizing sentences, staying on topic, or following the flow of a conversation. Importantly, recent work has suggested that up to 25% of

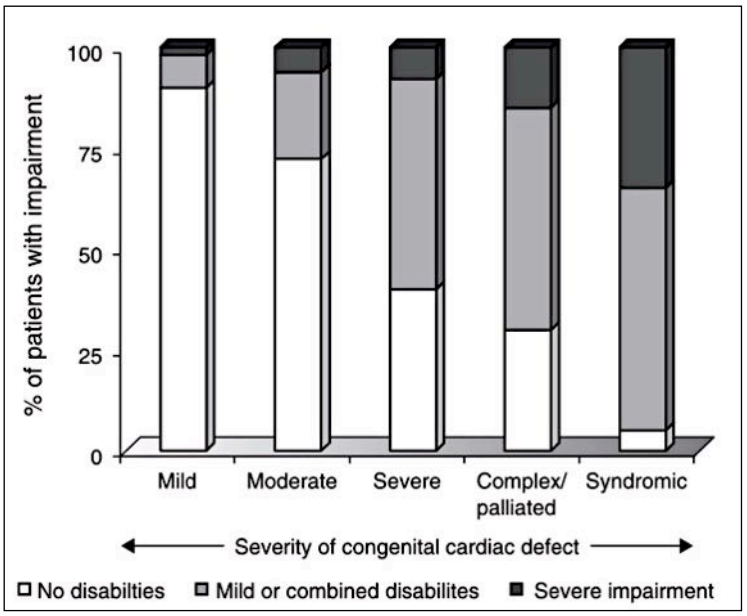

Figure legend: The frequency and severity of neurodevelopmental disabilities in children with congenital heart disease varies with the complexity of disease.

From Wernovsky G. Current insights regarding neurological and developmental abnormalities in children and young adults with complex congenital cardiac disease. Cardiology in the Young 2006;16 Suppl 1:92-104. With permission.

children with cCHD have some form of hearing loss after surgery, which substantially impacts the development of language and academic skills; a formal hearing evaluation should be considered as part of the routine follow-up of these children.

In addition to delays in expressive language, some preschool children with cCHD (at least 25%) have ongoing difficulties with motor skills, including large motor delays (clumsiness), fine motor delays (problems with buttoning, zipping, cutting), and visual-motor delays (drawing). Visual-motor integration relates to the ability to coordinate thoughts and images into motor action. In preschool and school age children, handwriting represents a particular challenge: seeing handwriting on the board, knowing that it's a particular letter, and getting the hand to make the letter can be very frustrating to an otherwise bright child. In many children, fine and gross motor skills improve by the time they enter school, though visual-motor problems remain prevalent.

By preschool age, problems with executive skills also begin to emerge. Executive function (EF) refers to a group of skills used to complete novel or complex tasks. In other words, these are not the "know how," but the "how you do it" skills, and become more important when we need to tackle something new or different – when we aren't on auto-pilot. Core components of EF include inhibition (being able to "put on the brakes" when needed), working memory (our mental chalkboard, where we keep track of and work with information "in our head"), and flexibility (being able to generate multiple solutions, change tactics when needed, and transition effectively between tasks/activities). These core skills allow us to initiate, plan, and organize our approach to tasks, and to regulate our

emotions and behaviors across situations. For example, preschoolers with cCHD may have difficulty with tantrums, transitions, following classroom routines, or remaining flexible in social situations.

School-Age and Beyond

As children with cCHD enter primary and secondary school in larger numbers, there is a growing recognition of a combination of challenges that may combine to cause academic and social problems. As we look more carefully at children with cCHD, there is a higher rate of diagnosis of Attention Deficit Hyperactivity Disorder (ADHD), with estimates ranging between 25%-53% of children showing symptoms of the disorder, compared to 7-10% of the general population. The core features of ADHD include problems with attention, hyperactivity, and impulsivity, along with executive dysfunction. There are also higher rates of learning disabilities and academic problems in children with cCHD.

Early delays in language, visual and motor skills, processing speed, and self-regulation may interact over time to contribute to increased rates of ADHD and learning disorders, and problems in school more generally. Problems with EF are of particular interest, as they are one of the more commonly reported concerns in children, adolescents, and adults with cCHD (with studies consistently finding that more than half of these children have concerns around some aspects of EF). EF is also known to strongly predict success in school (more so than "IQ" or early academic skills) and social relationships, and to strongly influence mental health and quality of life. That is, a child or teen with poorly developed EF may be bright and a strong reader, but struggle with tying together broader themes or "main ideas" when reading, or may have trouble effectively communicating while writing. They may master early math but have trouble with more complex math problem solving. They can struggle to complete work on time, procrastinate (since they have trouble knowing where to start), or forget to turn in completed work. This can lead to frustration as children, adolescents, and adults often fail to truly demonstrate otherwise strong skills in school or at work.

Finally, there are social-emotional challenges. Many children with cCHD have weaknesses with social skills and higher order language. There is an increased incidence of Autism, which is characterized by problems with social skills, communication, and flexibility. Problems with mood and anxiety are also common starting in school age, adolescence, and adulthood.

Despite these risks, there are many children with cCHD, even those with very complex medical histories, who do exceedingly well and do not seem to experience these challenges. It is important for us to investigate the "protective" factors from these individuals – in other words, what provides "resiliency" in the face of cCHD? In addition, there are many effective forms of intervention for ADHD, executive dysfunction, and learning disorders, and these can very much improve outcomes, especially when implemented early, though it should also be stated that it's never too late. Parents and providers should also work to identify and cultivate each child's strengths and talents, and to figure out how their child learns best. Because of this, the AHA and AAP recognize the importance of regular neurodevelopmental evaluations in this high-risk sample, so that problems can be identified and managed early.

Etiology

Although it is tempting to point at "one" feature as "the cause" of the above findings seen so commonly in cCHD, that would be a terrible oversimplification. The effects of cCHD on the developing brain of children are multiple, and cumulative over the early years of development.

Following conception, the closure of the neural tube and early brain development occurs at the same time that the heart forms, in the first trimester. In most cases, whatever causes CHD has "left its mark" on the heart by the end of the 8th week of gestation. In contrast, the brain continues to develop and mature throughout pregnancy (and beyond). Studies are accumulating, demonstrating that the abnormal circulation caused by cCHD in the fetus is likely responsible for some of the abnormalities in brain growth and development present at birth. Clearly, "congenital heart disease" and "congenital brain disease" are co-linked variables in many children. Does the same factor or factors that cause CHD also cause brain abnormalities as well? Is the brain "wired" the same way in children with CHD compared to normal? How does the abnormal fetal circulation put an abnormal fetal brain at greater risk for other stressors? Early work in this area was limited to post-natal findings such as microcephaly and neonatal neurological examinations. Subsequent work utilizing fetal Doppler ultrasound revealed abnormalities in cerebral vascular pulsatility suggesting cerebral vasodilation and a decrease in cerebral vascular resistance in left heart obstructive lesions, with some suggesting an elevation in cerebral vascular resistance in right-sided lesions. However, now that newer technologies such as Magnetic Resonance Imaging (MRI) in the fetus and newborn have become more routinely available, it has been noted that there is a mismatch of oxygen and likely substrate (glucose) delivery to the highly metabolically active brain of the developing fetus, particularly in the third trimester. Exciting developments in the understanding of placental development and altered placental function are on the horizon as well. The brain of many newborns with cCHD delivered at term appears 'immature'; several studies have shown that the brain of a full-term infant with cCHD has the complexity (or "maturity") of the brain of a 35-36 week gestation infant without cCHD. This has led to a paradigm shift over the past decade to encourage delivery as close to term (39-40 weeks) as possible, unless there are maternal or fetal reasons to recommend earlier delivery. Finally, genome-wide analyses and certain polymorphisms are being linked to both the prevalence of later school difficulties and cCHD, and also in the way the brain of the newborn responds to stressors such as cardiopulmonary bypass and postoperative care.

Importantly, many published studies exclude children with other known conditions which affect neurodevelopment, such as genetic syndromes, prematurity and additional congenital anomalies. Genetic syndromes and abnormalities on genetic screening, and/or additional congenital anomalies exist in up to 25% of neonates with cCHD. Finally, population studies of newborns with cCHD suggest a higher incidence of prematurity and "small for gestational age," possibly suggesting a role of placental insufficiency. The placenta may be inherently abnormal and low fetal cardiac output and oxygen delivery to the placental circulation may be a factor, again suggesting an interaction between the type of cCHD and its effect on oxygen delivery and cardiac output to the fetal-placental axis.

For neonates with cCHD after birth, multiple factors occur nearly simultaneously that make it extremely difficult to separate out their relative contributions to long-term outcomes. These factors include, but are not limited to: hypoxemia, low cardiac output, cardiopulmonary bypass, analgesic and anxiolytic medications, volatile anesthetic agents, paradoxical emboli (in children with right-to-left shunting), nutritional deficiencies, limited mobility and developmental stimulation in the early postoperative period, noise exposure, plastics and other toxins, prolonged mechanical ventilation and many more. In essentially all published studies, longer hospital Length of Stay (LOS) is related to worse long-term outcomes. It is highly likely that longer LOS represents a surrogate outcome variable for the additive and interactive causes mentioned above. Finally, the combined effects of a long stay in the intensive care unit and hospital on both the baby and the family, greatly increase the risk of Acute- and Post-Traumatic Stress Disorder in parents (see below).

In past research, many long-term neurodevelopmental findings were attributed to cardiopulmonary bypass (CPB, particularly its duration), pH management, deep hypothermic circulatory arrest, hematocrit, temperature, steroid use, modified ultrafiltration, and more. While these factors are certainly important to the brain and later development, recent work suggests that these effects are seen early in life, but

become minimal as the children develop. In the Boston Circulatory Arrest Study, the longest prospectively published study to date, deep hypothermic circulatory arrest (DCHA) was related to abnormal outcomes through age four, both DHCA and low flow CPB were each related to different types of abnormalities at age eight, and by age 16, none of the measured CPB variables had a significant effect on outcomes. Importantly, in many studies, CPB and intraoperative management are responsible for less than than 5% of the variability of long-term developmental outcomes. Perhaps the most important factor in cardiac surgery and recovery is the technical success of the operation. An anatomically and physiologically successful operation leads to improved postoperative oxygen delivery and a shorter length of stay in the hospital; we believe that this is more important than how long it takes to accomplish the operation or factors related to CPB.

Treatment

Thus far, research in the treatment of neurodevelopmental problems in patients with cCHD lags behind research in prevalence and etiology. For example, there is limited data at the current time to comment on the safety and efficacy of the psychotropic drugs (for example, stimulant medications for ADHD, anti-depressants, etc.) in children with cCHD, and this must be an individual decision with a child's cardiologist. Many of the medications currently available for children with structurally normal hearts slightly increase the risk of rhythm problems and high blood pressure; and some children with CHD may be at increased risk for rhythm disturbances when using these medications. It must be emphasized that no large study has determined the safety and efficacy of these drugs specifically in children with cCHD, or even if they work the same way as in children with structurally normal hearts. The decision to use medications to deal with behavioral issues or ADHD must be individualized to the child, balancing the unknown risks of these medications in children with CHD against the lifelong implications of academic and social difficulties. Close follow-up, planning and surveillance are warranted when beginning any new medication. Whether or not medication is used as a treatment tool, parents and families should be encouraged to seek out evidence-based therapies to treat speech-language and motor delays, executive dysfunction, and learning differences. Most often, it is the combination of medical and behavioral/therapeutic approaches that is most effective. Harnessing community resources, such as services and supports in the school system (e.g., individualized educational plans) is also critically important. Finally, one must address post-traumatic medical stress and family functioning, and evidence-based therapy for mood or anxiety disorders. Most researchers agree that this is a central component to increasing effectiveness of other interventions.

Some studies are underway investigating whether increasing oxygen delivery to the brain and/or placenta of a fetus with cCHD can be safely accomplished through maternal administration. Also, there is growing evidence in studies across the globe that treatments geared toward decreasing maternal worry and improving parental mental health show significant promise in improving long-term outcomes. These include prenatal counseling, pre- and post-operative support with clergy and palliative care teams, and increased contact with advanced practice nurses prior to and after hospital discharge.

Future Directions

In our opinion, the outlook for children with cCHD remains quite optimistic. Many are now adults and are engineers, nurses, doctors, social workers, and teachers; many are parents themselves, and lead happy, productive lives. Nonetheless, there are ongoing challenges for those of us who care for these children to improve overall quality of life. It is important to emphasize that long-term prospective studies, and cross-sectional studies in older adults with CHD represent management strategies from the 1970's-2000's, and there is a suggestion that there is some improvement in many areas of functioning for children born more recently. This is likely due to the many important and simultaneous improvements in the last two decades—including more frequent prenatal diagnosis, research into the developing brain before and after surgery, a better understanding of anesthesia and cardiopulmonary bypass, improved post-operative care, and the benefits of structured follow-up programs. A number of additional factors will ultimately contribute to the academic success of our children, including genomics and a personalized medicine approach to surgery and perioperative care.

It has also been learned that - not surprisingly - the stress of having a child with cCHD on parents and families is prevalent, occasionally severe and long-lasting. Importantly, taking steps to improve parental mental health (mindfulness techniques, PTSD therapy, etc.) improve both the parents and the child's long-term outlook. As is said when you board an airplane: "Put your own mask on first before helping others". We cannot over-emphasize the importance of self-care – both physically and mentally – for families affected by a child with cCHD.

Finally, the best way to improve the outcomes for future generations is a continued and long-term partnership between patients, parents, researchers, nurses, therapists, psychologists, physicians and many others. Advocacy by physicians, parents and patients at the government level for continued funding of research is crucial. We must continue to pursue the causes and treatment of heart disease in children, as well as the secondary effects on the brain and quality of life. Philanthropic contributions play a significant role in start-up funds for research as well. Finally, if families and children are willing, voluntary participation in clinical research studies remains the cornerstone of the process.

Summary of Current Findings, 2018

- In the absence of an associated structural brain abnormality or genetic syndrome, cognitive function (IQ, intelligence) is typically within the normal range for most children with CHD.
- Parental education, mental health and socioeconomic status are consistently the most strongly associated factors in the long-term outcomes for children with cCHD, rather than the specific type of CHD or its management. Of these, while the effects of low socio-economic status may be attenuated by participation in enrichment programs (e.g., early preschool, "headstart"), only parental mental health is truly modifiable.
- Early delays with language, motor, and visual motor skills are common in children with cCHD.
- Problems with executive function – which affects behavioral regulation and completion of complex tasks – are highly prevalent in cCHD, and may be the most important factor in long term success and health-related quality of life.
- There are higher rates of ADHD, learning disorders, and autism in children with cCHD.
- Some identified risk factors for academic and behavioral difficulties include highly complex CHD requiring multiple procedures, a long hospital stay, and family PTSD. Health-related quality of life is also affected by the number of medications necessary and number of doctor visits per year.
- The association between abnormal fetal oxygen and substrate delivery, open heart surgery and postoperative care with later cognitive, language, or behavior difficulties continues to be an active area of investigation.

Given these findings, The American Heart Association and American Academy of Pediatrics have recommended regular neurodevelopmental evaluations, in infancy, school age, and adolescence, for children with cCHD. Included below is a list of recent selected interdisciplinary references related to the diagnosis and treatment of neurodevelopmental disabilities in children with cCHD.

To learn more, please join us at the *7th Scientific Sessions of the Cardiac Neurodevelopmental Outcome Collaborative*, June 6-8, 2018 in Kansas City, USA. See http://bit.ly/CNOC18 for more details.

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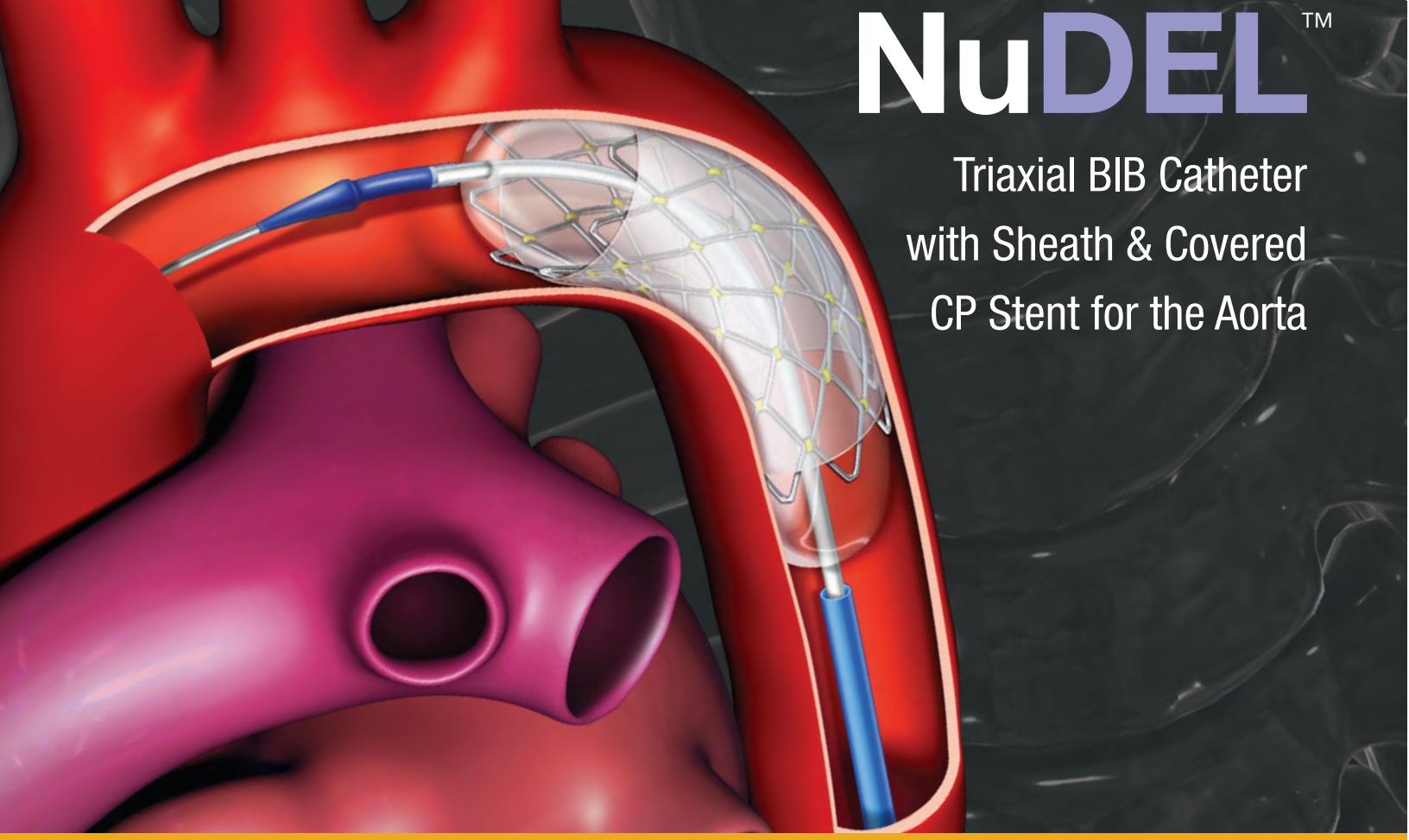

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Children with complex Congenital Heart Defects (cCHD) are now surviving neonatal and infant surgery with a frequency thought to be impossible only a generation ago. While advances in medicine and surgery have allowed the ability to "mend" children born with CHD, the increasing number of survivors has created a growing population of children in our primary and secondary school systems, and young adults entering the job force."

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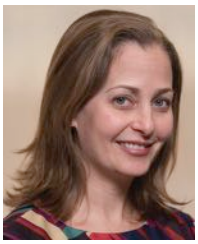

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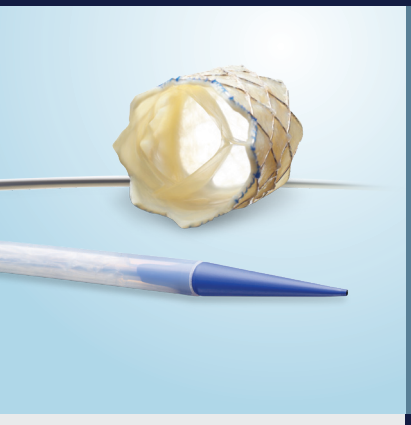


Melody™

Transcatheter Pulmonary Valve (TPV) System

Not intended to constitute medical advice or in any way replace the independent medical judgment of a trained and licensed physician with respect to patient needs or circumstances. Melody TPV is not suitable for all patients and ease of use, outcomes, and performance may vary. See the Instructions for Use for indications, contraindications, precautions, warnings, and adverse events.

*Melody Transcatheter Pulmonary Valve Study: Post Approval Study of the Original IDE Cohort

UC201809030a EN 04/2018

Confident with over

7

years of clinical data.*

The only transcatheter valve designed specifically for RVOT conduits and bioprosthetic valves. Thin leaftlets from naturally derived tissue open and close under minimal pressure. The flexible delivery system is designed for the right side of the heart and offers controlled, stepwise deployment of the valve with balloon-in-balloon technology.

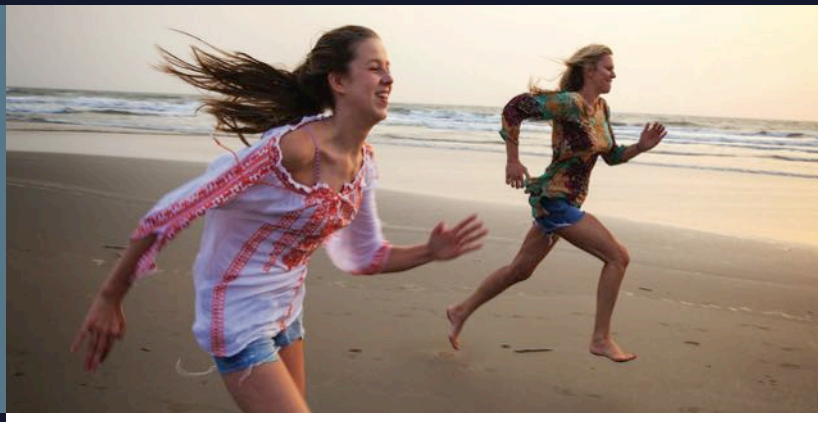
Melody TPV — The Right Design for Your Patients

Medtronic
Further, Together

RIGHT CHOICE.

Melody™

Transcatheter Pulmonary Valve (TPV) System



Not intended to constitute medical advice or in any way replace the independent medical judgment of a trained and licensed physician with respect to any patient needs or circumstances. Melody TPV is not suitable for all patients and ease of use, outcomes, and performance may vary. See the Instructions for Use for indications, contraindications, precautions, warnings, and adverse events.

Restoring lives for

11

years and counting.

The only transcatheter pulmonary valve specifically designed for RVOT conduits and bioprosthetic valves. The longest studied, with the largest body of clinical evidence at 7 years post-implant.* Over 11 years of implants, more than 12,000 patients' lives have been changed.

Melody TPV — The Right Choice for Your Patients

*Melody Transcatheter Pulmonary Valve Study: Post Approval Study of the Original IDE Cohort.

UC201809495 EN 02/2018

Medtronic
Further, Together

Melody™ Transcatheter Pulmonary Valve, Ensemble™ II Transcatheter Valve Delivery System

Important Labeling Information for the United States

Indications: The Melody TPV is indicated for use in the management of pediatric and adult patients who have a clinical indication for intervention on a dysfunctional right ventricular outflow tract (RVOT) conduit or surgical bioprosthetic pulmonary valve that has ≥ moderate regurgitation, and/or a mean RVOT gradient ≥35 mm Hg.

Contraindications: None known.

Warnings/Precautions/Side Effects:

- **DO NOT implant in the aortic or mitral position. Pre-clinical bench testing of the Melody valve suggests that valve function and durability will be extremely limited when used in these locations.**
- DO NOT use if patient's anatomy precludes introduction of the valve, if the venous anatomy cannot accommodate a 22 Fr size introducer, or if there is significant obstruction of the central veins.
- DO NOT use if there are clinical or biological signs of infection including active endocarditis. Standard medical and surgical care should be strongly considered in these circumstances.
- Assessment of the coronary artery anatomy for the risk of coronary artery compression should be performed in all patients prior to deployment of the TPV.
- To minimize the risk of conduit rupture, do not use a balloon with a diameter greater than 110% of the nominal diameter (original implant size) of the conduit for pre-dilation of the intended site of deployment, or for deployment of the TPV.
- The potential for stent fracture should be considered in all patients who undergo TPV placement. Radiographic assessment of the stent with chest radiography or fluoroscopy should be included in the routine postoperative evaluation of patients who receive a TPV.
- If a stent fracture is detected, continued monitoring of the stent should be performed in conjunction with clinically appropriate hemodynamic assessment. In patients with stent fracture and significant associated RVOT obstruction or regurgitation, reintervention should be considered in accordance with usual clinical practice.

Potential procedural complications that may result from implantation of the Melody device include the following: rupture of the RVOT conduit, compression of a coronary artery, perforation of a major blood vessel, embolization or migration of the device, perforation of a heart chamber, arrhythmias, allergic reaction to contrast media, cerebrovascular events (TIA, CVA), infection/sepsis, fever, hematoma, radiation-induced erythema, blistering, or peeling of skin, pain, swelling, or bruising at the catheterization site.

Potential device-related adverse events that may occur following device implantation include the following: stent fracture*, stent fracture resulting in recurrent obstruction, endocarditis, embolization or migration of the device, valvular dysfunction (stenosis or regurgitation), paravalvular leak, valvular thrombosis, pulmonary thromboembolism, hemolysis.

*The term "stent fracture" refers to the fracturing of the Melody TPV. However, in subjects with multiple stents in the RVOT it is difficult to definitively attribute stent fractures to the Melody frame versus another stent.

For additional information, please refer to the Instructions for Use provided with the product or available on http://manuals.medtronic.com.

CAUTION: Federal law (USA) restricts this device to sale by or on the order of a physician.

Important Labeling Information for Geographies Outside of the United States

Indications: The Melody™ TPV is indicated for use in patients with the following clinical conditions:

- Patients with regurgitant prosthetic right ventricular outflow tract (RVOT) conduits or bioprostheses with a clinical indication for invasive or surgical intervention, OR
- Patients with stenotic prosthetic RVOT conduits or bioprostheses where the risk of worsening regurgitation is a relative contraindication to balloon dilatation or stenting

Contraindications:

- Venous anatomy unable to accommodate a 22 Fr size introducer sheath
- Implantation of the TPV in the left heart
- RVOT unfavorable for good stent anchorage
- Severe RVOT obstruction, which cannot be dilated by balloon
- Obstruction of the central veins
- Clinical or biological signs of infection
- Active endocarditis
- Known allergy to aspirin or heparin
- Pregnancy

Potential Complications/Adverse Events: Potential procedural complications that may result from implantation of the Melody device include the following: rupture of the RVOT conduit, compression of a coronary artery, perforation of a major blood vessel, embolization or migration of the device, perforation of a heart chamber, arrhythmias, allergic reaction to contrast media, cerebrovascular events (TIA, CVA), infection/sepsis, fever, hematoma, radiation-induced erythema, pain, swelling or bruising at the catheterization site.

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For additional information, please refer to the Instructions for Use provided with the product or available on http://manuals.medtronic.com.

The Melody Transcatheter Pulmonary Valve and Ensemble II Transcatheter Delivery System has received CE Mark approval and is available for distribution in Europe.

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Medtronic

Specialty Review in Pediatric Cardiology - Board Review CME Course - August 13th-17th, 2018, Chicago, IL

By Maria Serratto, MD

With the 2018 "*Specialty Review in Pediatric Cardiology Course*" approaching, I am thinking back to its beginning. Even though pediatric cardiology in the seventies was rapidly expanding in diagnostic and surgical techniques, candidates for board examination had to rely on repeated visits to the medical library to update their knowledge and refresh the experience acquired during their training. A preparatory curriculum was clearly needed.

Starting in 1976 I organized the first *"Specialty Review in Pediatric Cardiology"* run under the auspices of the Cook County Graduate School of Medicine of Chicago, with faculty drawn from local universities. That year the program was two days in length and was attended by approximately 30 registrants from throughout the United States.

Over the years the course expanded to its present 5-day format, attracting attendees not only from the US but from abroad as well, with a distinguished national planning committee and faculty.

"Over the years the course expanded to its present 5-day format, attracting attendees not only from the US but from abroad as well, with a distinguished national planning committee and faculty. Perhaps the most important recognition to the quality and continuing relevance of the course came in 2010 when sponsorship was assumed by the American Academy of Pediatrics Section on Cardiology and Cardiac Surgery in collaboration with the Society of Pediatric Cardiology Training Program Directors."

Perhaps the most important recognition to the quality and continuing relevance of the course came in 2010 when sponsorship was assumed by the *American Academy of Pediatrics Section on Cardiology and Cardiac Surgery* in collaboration with the *Society of Pediatric Cardiology Training Program Directors.*

Technological advances have likewise contributed to the course value. An online syllabus now makes it possible for presented slide material to be viewed in full-color full-page format. Practice examination Q&A exercises following each presentation are supported by audience-response system technology. Presentations are recorded to produce a "watch-it-again" option, available shortly after the course and a CM- accredited DVD version of the course released soon after the end of the course. An online option for those wishing to earn MOC credit was introduced in 2014.

Continuing advances in the specialty and expanding needs of our constituency have certainly contributed to course growth as well, especially in recent years as those who are already board certified prepare to meet re-certification requirements and practitioners strive to remain current in our ever-expanding field.

The past 42 years have been a rewarding journey for me and the many others who have contributed to the success of the course, as we have had the honor to come to know hundreds of fine specialists and interact with them over the span of their careers. Whether you are new to the "*Specialty Review in Pediatric Cardiology Course"* or a member of our distinguished alumni, we look forward to having you with us in Chicago this coming August 13-17.

For details on the upcoming 2018 offering, please visit the course website: http://pediatriccardiologycourse.com.

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Laurie R. Armsby, MD, FAAP, FSCAI
Course Co-Director
David W. Brown, MD, FAAP
Antonio G. Cabrera, MD, FAAP
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Medical News, Products & Information

Compiled and Reviewed by Kate Baldwin, Special Projects Editor

Two-Year Feasibility Study Results Encouraging with Medtronic Harmony™ Transcatheter Pulmonary Valve

On April 26, 2018, Medtronic plc (NYSE: MDT) today announced two-year outcomes for the Harmony™ Transcatheter Pulmonary Valve (TPV) from its early feasibility study. Presented at the *Society for Cardiovascular Angiography and Interventions (SCAI) 41st Annual Scientific Sessions*, data from 18 patients followed out to two years revealed the Harmony TPV showed solid valve function and no Paravalvular Leak (PVL).

"Following the one-year feasibility outcomes, we are encouraged to see the Harmony valve continues to show positive outcomes for patients two years post-implant," said Matthew J. Gillespie, MD, cardiologist at The Cardiac Center at Children's Hospital of Philadelphia, who presented the data at the meeting. "We are optimistic that these early outcomes will be a strong indicator of the types of results that we might expect to see from our pivotal study, which is currently enrolling."

Designed to offer a treatment alternative for patients with Congenital Heart Disease (CHD), the Harmony TPV is being studied in CHD patients born with Right Ventricular Outflow Tract (RVOT) anomalies who undergo a surgical repair early in life. For these patients, who account for approximately 80% of CHD patients born with RVOT anomalies, the Harmony TPV provides a less invasive option to help restore normal valve function later in life.

Consistent with one-year outcomes presented at TCT16, patients enrolled in the Harmony TPV early feasibility study who have now been followed out to two years (N=18) continued to experience strong hemodynamics (blood flow), with 86.7 percent of patients having no/trace pulmonary regurgitation (PR) at two years. Mean gradients were consistent and stable at two years follow-up, and there were no paravalvular leaks reported. Two patients experienced tissue growth within the stent frame and were treated successfully with a transcatheter valve-in-valve procedure with the Melody™ TPV.

"It's important that these patients have access to a less invasive non-surgical option, and the Harmony TPV is uniquely designed to adapt to a wide variety of patient anatomies," said Pieter Kappetein, MD, PhD, VP and Chief Medical Officer of the Structural Heart business, which is part of the Cardiac and Vascular Group at Medtronic. "Medtronic remains committed to Congenital Heart Disease, and we continue to look for ways to expand therapeutic options and improve outcomes for these patients, from their first surgeries as young children through their years as active, high-functioning adults.

The Harmony TPV is available for investigational use only. Harmony Pivotal IDE Study is treating up to 40 patients at approximately 15 sites in the U.S., Canada, and Japan. Medtronic has a long-standing commitment to Congenital Heart Disease and introduced the first transcatheter heart valve available anywhere in the world in 2006 – the Melody TPV – which has been implanted in more than 12,000 patients worldwide.

In collaboration with leading clinicians, researchers and scientists worldwide, Medtronic offers the broadest range of innovative medical technology for the interventional and surgical treatment of cardiovascular disease and cardiac arrhythmias. The company strives to offer products and services that deliver clinical and economic value to healthcare consumers and providers around the world.

Medtronic plc (www.medtronic.com), headquartered in Dublin, Ireland, is among the world's largest medical technology, services and solutions companies – alleviating pain, restoring health and extending life for millions of people around the world. Medtronic employs more than 84,000 people worldwide, serving physicians, hospitals and patients in more than 160 countries.

B.Braun Interventional Systems Launches Expanded CP Stent® Portfolio in Collaboration with NuMED, Inc.

B.raun Interventional Systems Inc. (BIS) in collaboration with NuMED Inc., recently announced the Food and Drug Administration pre-market approval and U.S. commercial launch of an expanded size offering and new indication for the Cheatham-Platinum (CP) Stent portfolio.

'The first and only large diameter, balloon expandable stent approved for treatment of coarctation of the aorta and RVOT conduit disruptions in the U.S.

The CP Stent became available in the U.S. market in 2016 for treatment of coarctation of the aorta with BIS entering into an exclusive U.S. distribution agreement with the manufacturer, NuMED Inc. Building upon the success of the CP Stent in the market, and in an effort to address unmet clinical needs, additional sizes and indications have been pursued.

The newly approved indication applies to the Covered and Covered Mounted CP Stent™ configurations for the treatment of right ventricle to pulmonary artery (right ventricular outflow tract, RVOT) conduit disruptions. These disruptions are identified during conduit pre-dilatation procedures performed in preparation for transcatheter pulmonary valve replacement (TPVR). The pivotal trial associated with this approval, PARCS (Pulmonary Artery Repair with Covered Stents), is publicly available on the ClinicalTrials.gov site for more details.

In addition to the new indication, this latest approval also includes additional sizes for the CP Stent portfolio. The expanded size offering includes CP Stent configurations expandable up to 30 mm in diameter and lengths up to 6 cm. All sizes and configurations of the Covered CP Stent are now approved for the treatment of both coarctation of

the aorta and RVOT conduit disruptions, while the bare CP Stent configurations are only approved for the treatment of coarctation of the aorta.

“Over the first two years of U.S. commercial availability, the CP Stent has demonstrated an impressive record of clinical utility in some of the most challenging interventional cases. The recent portfolio expansion for larger diameters, longer lengths, and a new indication are significant developments for this critical product line,” said Peter Flosdorf, B. Braun Interventional Systems Engineering Manager. “We are proud to collaborate with NuMED to provide physicians with indispensable tools for the treatment of congenital heart defects.”

"The approval of the additional sizes and clinical applications for the CP Stent line is an exciting milestone for NuMED that further delivers on our commitment to improve patient care by bringing to market innovative solutions to unmet clinical needs within the structural heart community," said Al Tower, President of NuMED, Inc. “We are pleased to continue our longstanding collaboration with the B. Braun Interventional Systems team to help us support the U.S. market for congenital heart interventions."

About B. Braun Interventional Systems
BBraun Interventional Systems offers interventional solutions designed with the patient in mind. Many of the products offered have been developed in response to the needs of physicians, technicians, and nurses. The company is committed to delivering safety, precision and convenience to interventional procedures. B. Braun Interventional Systems Inc. is part of the B. Braun Group of Companies in the U.S., which is headquartered in Bethlehem, Pa., and includes B. Braun Medical Inc., Aesculap®, and CAPS®.

Globally, the B. Braun Group of Companies employs more than 61,000 employees in 64 countries. Guided by its Sharing Expertise® philosophy, B. Braun continuously exchanges knowledge with customers, partners and clinicians to address the critical issues of improving care and lowering costs. To learn more about B. Braun Interventional Systems Inc., visit www.bisusa.org/about-us.

About NuMED, Inc.
Since 1982, NuMED has been developing, manufacturing and delivering innovative cardiovascular medical products for the smallest of patients to adults with heart defects.

Headquartered in Hopkinton, NY, NuMED’s mission is to improve the quality of patient care and the productivity of health care by developing and advocating less-invasive medical devices and procedures. They are committed to continually refining their existing products, and researching new technologies that can reduce risk, trauma, cost, procedure time and the need for aftercare. To learn more about NuMED, visit www.numedforchildren.com.

Terumo Aortic Announces European Launch of Relay®Pro THORACIC Stent Graft System at Charing Cross s 2018

'Low profile without compromise'

Terumo Aortic announced the European limited market release of the RelayPro Thoracic Stent-Graft System at the 2018 Charing Cross conference. RelayPro is a low profile, next generation device designed to expand the treatment of Thoracic Endovascular Aortic Repair (TEVAR) to patients with smaller access vessels. Utilizing the same stent design, material, and Dual Sheath Technology of the proven RelayPlus with a 3 to 4 Fr reduction in outer profile, RelayPro delivers the accuracy, control and confidence of the RelayPlus without compromising device integrity and durability.

RelayPro offers physicians a wide range of diameters, lengths, tapers, and proximal configurations. Available in both Bare Stent and Non-Bare Stent (NBS) versions, RelayPro can be individualized to meet the specific anatomical needs of patients.

Mark Miles, Global VP of Marketing at Terumo Aortic, said: “By combining the proven stent design and material of RelayPlus with a lower outer profile, RelayPro enables percutaneous access to treat a larger patient population. This advancement not only expands patient applicability but will help improve access site complications and ultimately reduce the burden of rising global healthcare costs.”

RelayPro is currently enrolling in multiple trials in U.S. and Japan for treatment of Descending Thoracic Aortic Aneurysms, Acute Complicated Type B Thoracic Aortic Dissection, and Blunt Aortic Trauma.

Terumo has combined Bolton Medical and Vascutek to power a dedicated approach focused on aortic innovation. With locations in Glasgow, Scotland and Sunrise, Florida, the integrated company offers advanced technologies such as surgical grafts, hybrid grafts and catheter-based stent graft systems to meet the unique needs of each patient and transform the treatment of aortic disease.

Child Life Specialists Play Key Role in Pediatric Hospital Care

Newswise —“For many children, the hospital can be a scary place,” said Linda Nicolotti, PhD, Director of

Pediatric Psychology at Brenner Children's Hospital, part of Wake Forest Baptist Medical Center.

"A lot depends on why they're here, how uncomfortable they are with their medical condition, how old they are, their developmental level, their personality characteristics, their coping skills and other factors. But all in all, hospitalization is often a very stressful experience for children."

That presents a challenge above and beyond providing medical care at children's hospitals, which generally serve patients from infancy to age 18 whose conditions range from minor to life-threatening and whose stays run from overnight to weeks or even months. And that challenge becomes more formidable during the holiday season.

"Holidays can be particularly hard for hospitalized kids and their families," Nicolotti said. "If a child is in the hospital, they're taken away from the annual routines and special activities of the season. Depression and anxiety are fairly common among children with health issues, particularly those that require them to be hospitalized, and the holidays are usually a more difficult time for children to be here."

"That's why we do all the things we do in December," said Cindy Mahan, Manager of the Child Life Department at Brenner Children's, a 144-bed facility that covers six floors of a tower on Wake Forest Baptist's main campus and admits more than 5,000 young patients a year.

Mahan and her staff of five certified Child Life Specialists and one assistant are dedicated to helping children and their families cope with all aspects of hospitalization and making their experiences at the hospital as positive as possible.

During the month of December, that includes "decking the halls." Christmas trees and other seasonal decorations are placed in all of Brenner's inpatients units, activity rooms and common areas.

"We try to create an environment that, while it's not home, is as festive as it can be," Mahan said.

*The holiday menu includes events, too: "*There are so many things happening in December at school, church and in the community that don't happen at any other time of year, and if you're in the hospital you're not able to participate," Mahan said. "So we try to provide opportunities that are similar to or maybe even more exciting than what the children would do normally."

Among these are three different visits from Santa Claus during the month. And on Christmas morning, all patients wake up to find that Santa has visited and left each of them a large gift bag full of age- and gender-specific presents.

All the decorations, events and gifts are made possible by direct donations of items and funds to the Child Life Department and contributions to Friends of Brenner, a volunteer advocacy and fundraising organization that supports the children's hospital.

"We have an incredibly generous community," said Mahan, who joined Wake Forest Baptist in 1978. "This is definitely our busiest time of the year for donations, but what we receive around Christmas also supports what we do for the children throughout the year."

That list includes: activities around Easter, Halloween and other holidays; birthday parties for individual patients; an off-site prom for teenagers in the Hematology/Oncology Unit; appearances by sanctioned "Star Wars" characters and window washers dressed in superhero costumes; and visits by members of Wake Forest University athletic teams.

The Child Life Department also maintains five age-appropriate activity rooms, an outdoor terrace with a garden and playground equipment, and a stockpile of toys, games, electronics and other items for patients' in-room use.

But it's not all about parties and playtime:

The Child Life program includes weekly visits by therapy dogs and other therapeutic activities. The staff specialists have clinical responsibilities, including: preparing children for medical procedures and treatments; conducting pre-surgery tours; teaching strategies to reduce anxiety and enhance cooperation with care providers; providing support and alternative focus before, during and after medical procedures; and offering information and support to patients' parents, siblings and other family members.

"It's really valuable to have a lot of psychosocial support for children while they're in the hospital," Nicolotti said. "Psychological issues can definitely exacerbate an ongoing medical problem, and relieving those problems can have positive effects on health."

Research studies have shown that child life programs and pediatric psychology services are associated with improved quality and outcomes in care, increased patient and family satisfaction, shorter hospital stays, decreased use of sedatives and pain relievers, greater adherence to "doctor's orders" and better overall health and well-being. The American Academy of Pediatrics has stated that child life services are "an important component of pediatric hospital-based care."

"If we have done our job well," Mahan said, "patients will have some positive memories of their hospitalization and will have learned that they can manage stressful situations both in the hospital and out."

Study Finds Children with Heart Disease Are Being Let Down by a Lack of Clinical Trials

Newswise — Less than 1% of UK children born with Congenital Heart Disease (CHD) are enrolled in clinical trials looking to improve treatments, research funded by the British Heart Foundation and led by the University of Birmingham and Birmingham Children's Hospital has found.

The study, published in the *European Journal of Cardio-Thoracic Surgery*, is the first systematic review of its kind into clinical trials in children's heart surgery.

The researchers analysed all 333 clinical trials published world-wide between 1st January 2000 and 31st August 2016 on surgery for CHD - heart conditions that develop in the womb and the most common type of birth defect. They found only 10 clinical trials (3%) were conducted in the UK in this time, none of which were Phase III trials - large, influential trials needed to change treatments or guidelines.

The researchers also found that only 431 out of the estimated 65,000 (<1%) children who underwent heart surgery in the UK in this timeframe were enrolled in a clinical trial. In comparison, 70% of children suffering from cancer are enrolled in Phase III clinical trials.

Although recent advances mean most children diagnosed with a CHD grow up to become adults, many face the prospect of multiple surgical operations, and sadly, around 400 children each year still die before they reach school age.

Poor recruitment was not able to explain the lack of clinical trials, with over 87% of trials able to recruit sufficient children. However, there are many different types of CHD, and it can be difficult for single hospitals to see enough of a particular type of the disease to carry out a meaningful trial.

Researchers suggest that one solution to this issue would be to establish a CHD research network which would allow researchers in all centres in the UK to collaborate and carry out research into the rarest types of CHD.

Lead author Mr. Nigel Drury, of the Institute of Cardiovascular Sciences at the University of Birmingham, and Consultant in Paediatric Cardiac Surgery at Birmingham Children's Hospital, said, "The surgery available for children with heart problems has improved dramatically over the past twenty years."

"However, by not carrying out large-scale, cutting-edge clinical trials to continually improve surgeries, we're letting down the thousands of children born in the UK each year with heart problems."

"As a Congenital Heart Disease community, we have a responsibility to provide scientific leadership and work together to conduct well-designed, rigorously conducted, multi-centre clinical trials to improve the outcomes of surgery for our patients and their families."

The startling research is being highlighted as part of the BHF's Christmas Appeal, which aims to raise £750,000 for life saving research towards CHD, which affects around 4,000 UK children each year.

Professor Sir Nilesh Samani, Medical Director at the British Heart Foundation, said, "For many children with Congenital Heart Disease, the only treatment available is surgery. It can be a difficult choice for parents to agree to their child participating in research. However, the only way we can improve the range and quality of treatments for these children is through clinical trials."

"This study shows that we can and should do better if we are to improve the treatment and outcomes of children with Congenital Heart Disease."

For more information, visit bhf.org.uk.

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[1] "International Multicentre Clinical Device Investigation on Safety and Effectiveness of the Nit-Occlud® Lê VSD Spiral Coil System for VSD Occlusion" (clinicatrials.gov identifier NCT00390702).

[2] "The Nit-Occlud® Lê VSD Registry", publication in preparation.