Navigating the FDA Medical Device Regulatory Pathways for Pediatric Lower-Limb Exoskeleton Devices

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Abstract — **There have been significant advances in the technologies for robot-assisted lower-limb rehabilitation in the last decade. However, the development of similar systems for children has been slow despite the fact that children with conditions such as cerebral palsy (CP), spina bifida (SB) and spinal cord injury (SCI) can benefit greatly from these technologies. Robotic assisted gait therapy (RAGT) has emerged as a way to increase gait training duration and intensity while decreasing the risk of injury to therapists. Robotic walking devices can be coupled with motion sensing, electromyography (EMG), scalp electroencephalography (EEG) or other non-invasive methods of acquiring information about the user's intent to design Brain-Computer Interfaces (BCI) for neuromuscular rehabilitation and control of powered exoskeletons. For users with SCI, BCIs could provide a method of overground mobility closer to the natural process of the brain controlling the body's movement during walking than mobility by wheelchair. For adults there are currently four FDA approved lower-limb exoskeletons that could be incorporated into such a BCI system, but there are no similar devices specifically designed for children, who present additional physical, neurological and cognitive developmental challenges. The current state of the art for pediatric RAGT relies on large clinical devices with high costs that limit accessibility. This can reduce the amount of therapy a child receives and slow rehabilitation progress. In many cases, lack of gait training can result in a reduction in the mobility, independence and overall quality of life for children with lower-limb disabilities. Thus, it is imperative to facilitate and accelerate the development of pediatric technologies for gait rehabilitation, including their regulatory path. In this paper an overview of the U.S. Food and Drug Administration (FDA) clearance/approval process is presented. An example device has been used to navigate important questions facing device developers focused on providing lower limb rehabilitation to children in home-based or other settings beyond the clinic.**

I. Introduction

Recent years have seen great advances in the development of neurotechnology, including robotics, for adult lower-limb and neuromuscular rehabilitation [1-3]. During the same time, the development in the pediatric population has not kept pace. Advances in gait therapy technology for children such as Robotic Assisted Gait Therapy (RAGT) have proved to be beneficial to users and therapists, but due to their size and cost are primarily limited to clinical settings. This can result in reduced dosages of gait therapy and slow rehabilitation progress. Access to this technology in home settings could accelerate the benefits seen from using rehabilitation devices and allow children to live more independent lives.

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To encourage developers of pediatric rehabilitation technology in their pursuit to provide gait therapy outside of rehabilitation facilities, an overview of the FDA submission process, focused on pediatric rehabilitation, is provided. A device currently under development at the University of Houston [4-5] is used as a case study for the FDA regulatory path assessment. The device may serve as diagnostic tool, mobility assistant and rehabilitation aide. The device can also be augmented with electroencephalography (EEG) signals to create a Brain-Computer/Machine Interface (BCI/BCM) for intent detection, neuromuscular rehabilitation and mobility [6].

To the best of the knowledge of the authors, there are no FDA cleared/approved brain-computer interfaces (BCI) for pediatric users that incorporate powered lower-limb rehabilitation technology. The example presented herein will focus on the regulatory aspects from the perspective of the device and emergent pediatric brain-computers interfaces.

II. Robotic Assisted Gait Therapy and Example Device Background

A. Pediatric Robotic Assisted Gait Therapy

Gait therapy is commonly prescribed for children with motor neuron-related and neuromuscular conditions affecting their lower-limbs. Traditional gait therapy employs manual articulation in which a child is suspended in a body-weight support harness above a treadmill and physical therapists manually provide the force for the lower limbs to complete corrective or therapeutic gait cycles (Figure 1).

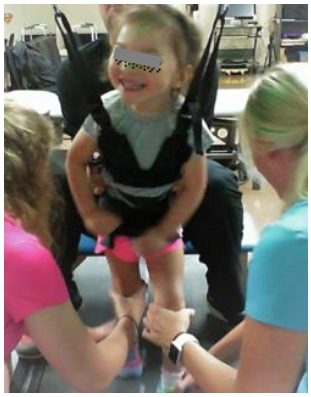

Figure 1. Manual articulation by physical therapists. Photo reprinted with permission [7]

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This type of therapy can be physically demanding and even lead to injury for therapists. An investigation into work-related injuries for occupational and physical therapists found an annual incidence rate of 16.5 and 16.9 injuries per 100 full-time workers among occupational therapists and physical therapists respectively. These rates are similar to those for workers employed in heavy manufacturing, and more than half of the therapist injuries are caused by transfer lifts and manual therapy [8]. One of the most significant advances of the last decade for gait therapy has been the use of robotics. Robotic assisted gait therapy allows for increased training duration, more repeatable gait patterns, and an increased objectivity to tracking the rehabilitation progress provided by electronic sensors and other data collected during training [9]. It also aids in preventing injuries of occupational and physical therapists. Reported benefits of RAGT in pediatric populations include improvements in gait speed and performance on the 6-minute walk test [10-12], improvements in the timed-up-and-go (TUG) test [12], improvements in overall walking and standing ability [13], improved hip kinematics and 10-meter walk test performances (reported improvements were still present during a one month follow-up) [14], reduction in the metabolic cost of walking [15] and reduction of crouch gait and postural improvements with outcomes equivalent to those reported after invasive orthopedic surgery [16]. RAGT has also been shown to promote motor learning and influence neuroplasticity [17-18].

There are currently four powered lower-limb exoskeleton devices cleared by the FDA for adults with SCI as Class II devices. They are: **ReWalk Personal** (Argo Medical Technologies Ltd, Yokneam Ilit, Israel) [19], **Indego** (Parker Hannifin Corp., Cleveland, OH, USA) [20], **Ekso GT** (Ekso Bionics Ltd., Richmond, VA, USA) [21] and the most recent to be cleared is **HAL** (CYBERDYNE Inc. Tsukuba, Japan) [22] (Figure 2). While overground powered exoskeletons are available on the market for adults, the options for children have been limited to passive walkers or large treadmill-based driven gait orthoses such as the Lokomat (Hocoma AG, Switzerland) [23] seen in Figure 3. While passive walkers allow for overground walking, they do not have a way to customize the gait pattern to provide rehabilitation from a pathological gait to one that is metabolically less expensive for the child. The Lokomat is able to provide walking assistance and allows for customizable gait patterns. In studies involving pediatric users, the Lokomat has been shown to provide improvements in gait speed and performance on the 6-minute walk test [10].

One example of the efforts to advance the science and clinical practice of rehabilitation robotics is the Advanced Robotic Therapy Integrated Centers (ARTIC) Network, which listed data from 595 children and adults with conditions that limited their walking ability (e.g., cerebral palsy, spinal cord injury, and various other diagnoses) and the outcomes of their robotic rehabilitation therapy. This large-scale, multi-site effort aims to exploit variations in practice to learn more about current clinical applications and outcomes of this therapy [24]. However, due to the large size and high device cost, the Lokomat is primarily constrained to clinical settings. Thus, there is a need for designing pediatric specific devices that can be used outside of clinical settings to provide increased

Figure 2. HAL exoskeleton from Cyberdyne Inc. Reprinted from {https://www.cyberdyne.jp/english/products/fl05.html*} with permission*

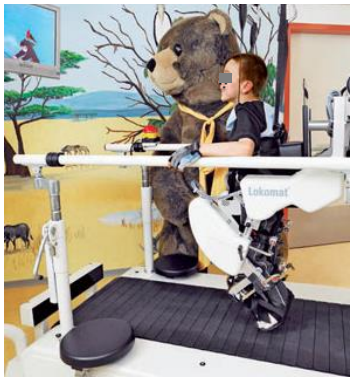

Figure 3. Pediatric Hocoma Lokomat. Reprinted with permission

dosages of gait training for children on a daily basis. With this need in mind, the pediatric lower extremity gait system (P-LEGS) [4] was developed (Fig. 4).

B. Example Device Description

The P-LEGS powered lower-limb orthosis is designed for children with motor disabilities or other conditions affecting their ability to walk independently and serves as walking pattern rehabilitation platform, mobility assistant and gait analysis/diagnostic tool. The modular device has a total of six motors to provide sagittal plane movement in the hip, knee and ankle joints of each leg and two non-motorized degrees of freedom at the hips to allow for weight shifting during walking. The walking pattern is customizable on a joint-by-joint basis to accommodate the unique needs of each child within the target populations [4-5].

Customized braces can be used interchangeably with the same actuator units and are located at each thigh and shank. The braces are 3D printed, based on 3D scans of the child's legs, and can be reinforced with a variety of materials (e.g., carbon fiber and fiberglass) to ensure strength in a lightweight form factor [25]. Figure 5 displays the method by which the braces are created and incorporated into the device.

Figure 4. Pediatric Lower Extremity Gait System. Reprinted from {https://pediatricexo.wordpress.com/about/} with permission

This device, with the addition of the custom braces, is technologically similar to the adult exoskeletons except that P-LEGS has active ankle actuators, is designed to grow with the child through the use of custom braces, and can interface with automated intention detection systems, including BCI/BMI systems.

However, the user populations for which the adult devices received FDA approval/clearance is persons with spinal cord injury or stroke while the target populations for the pediatric device include children with cerebral palsy, spina bifida, and other conditions that limit mobility. This difference in populations (age and conditions) may result in different user needs and affect the level of risk involved with the use of the device. For this reason, the FDA pathway could be different than if it were another adult-scale device for spinal cord injured users.

III. FDA Submission Pathways

In this section, FDA submission pathways are presented and discussion of each pathway's unique features and the viability of the pathway for the P-LEGS device is assessed. Information on important concepts such as predicate devices, substantial equivalence, indications for use versus intended use and special controls is also be provided.

A. Regulatory Pathways and Terminology

Figure 6 contains examples of devices within each of the three FDA designated classes and which class or classes may require controls – special or general and which may be eligible for exemptions. High-risk (Class III) devices may be so classified because they either sustain or support life, are implanted or present a potential risk of serious injury if they malfunction.

For a device to qualify for the 510(k) pathway, the device must be shown to be substantially equivalent to a device that has already been cleared by the FDA for marketing and can therefore be used as a predicate device for subsequent submissions. If a substantial equivalence determination is made, then the new device may be cleared for market.

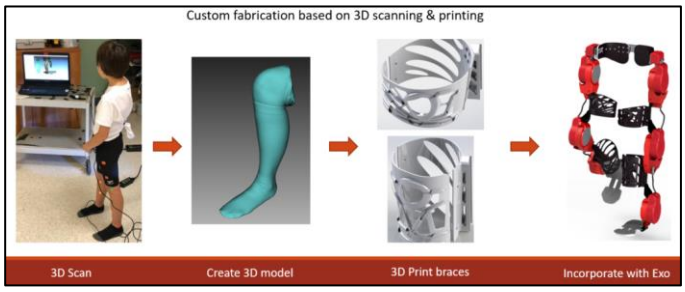

Figure 5. Brace development and incorporation with device. Reprinted from {https://pediatricexo.wordpress.com/about/} with permission

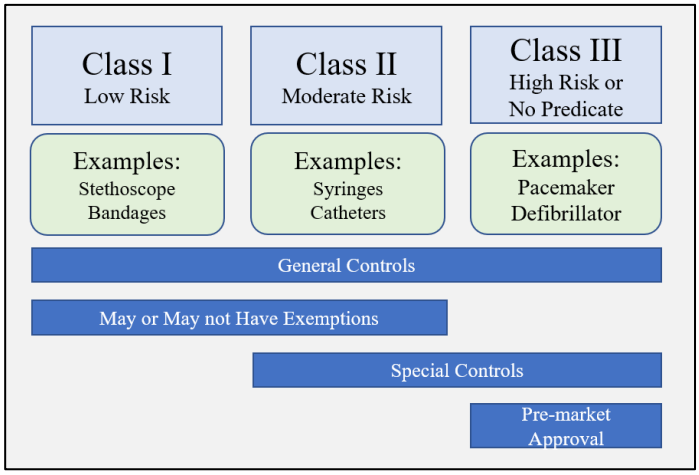

Figure 6. FDA regulatory pathways for medical devices.

B. Predicate Devices and Substantial Equivalence

As mentioned in the previous section, a predicate device is one that has passed through the FDA regulatory process and is lawfully on the market and is similar to the new devices coming to market. On page seven of the guidance document issued by the FDA titled: *The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications,* the FDA refers to section 513(i) of the FD&C Act and the term "substantially equivalent" or "substantial equivalence" means, with respect to a device being compared to a predicate device, that the device has the same intended use as the predicate device and that the Secretary by order has found that the device:

- has the same technological characteristics as the predicate device, or
- (I) has different technological characteristics and the information submitted that the device is substantially equivalent to the predicate device contains information, including appropriate clinical or scientific data if deemed necessary by the Secretary or a person accredited under section 523, that demonstrates that the device is as safe and effective as a legally marketed device, and (II) does not raise different questions of safety and effectiveness than the predicate device.

The term "different technological characteristics" means, with respect to a device being compared to a predicate device,

that there is a significant change in the materials, design, energy source, or other features of the device from those of the predicate device. For guidance on finding and effectively using a device as a predicate for a submission see [27]. Once a similar device has been found, the FDA has provided questions to guide device manufacturers through the process of determining if the device may qualify as a predicate for the submission. Table 1 summarizes the key questions.

Two additional important ideas are *indications for use* and *intended use.* These two terms are defined by the FDA as:

- **Indications for use** – The disease or condition the device will diagnose, treat, prevent, cure or mitigate, including a description of the patient population for which the device is intended.
- **Intended use** – The general purpose of the device or its function. The intended use of a device encompasses the indications for use.

TABLE I. QUESTIONS FOR DETERMINING SUBSTANTIAL EQUIVALENCE

Questions	
1	Is the predicate device legally marketed?
2	Do the devices have the same intended use?
3	Do the devices have the same technological characteristics?
4	Do the different technological characteristics of the devices raise different questions of safety and effectiveness?
5	Are the proposed scientific methods for evaluating the effects on safety and effectiveness due to the new/different characteristics acceptable?
6	Do the performance data demonstrate substantial equivalence?

If the answer to questions 1-3 is 'yes', then substantial equivalence can be determined. In the event that the answer to questions 1-2 is 'yes', but 'no' to 3, then use questions 4-6 to evaluate SE. The answer must be 'yes' to questions 4-6 for the device to be SE to the predicate. For additional information on predicate devices see the FDA guidance document, *The 510(k) Program: Evaluating Substantial Equivalence in Premarket Notifications [510(k)]*.

C. Predicate device example

In the case of the P-LEGS powered exoskeleton, the technology is similar to the adult-scale exoskeletons - albeit it contains ankle actuators which are not present in the current cleared devices used for SCI and stroke survivors - but the target populations are different. In this case a possible predicate device could be the ReWalk powered exoskeleton. The ReWalk could potentially be used as the predicate device because it was the first of its type to be approved by the FDA. If another device manufacturer had sought approval prior to ReWalk, then they would have had to pass through the De Novo process and, after approval, would act as the predicate. There is typically only one predicate device for a certain category.

ReWalk:

- Year De Novo Granted: 2013
- Regulation Number: 21 CFR 89.3480
- Classification: II
- Product Code: PHL
- Device Type: Powered Exoskeleton

Referring to the questions in Table1, the answers to questions one and three are 'yes', but the answer to question two includes both the intended use and the indications for use because the intended use of a device encompasses the indications for use. The indications for use as listed in the De Novo application for ReWalk are as follows:

- The Argo ReWalk orthotically fits to the lower limbs and part of the upper body and is intended to enable individuals with spinal cord injury at levels T7 to L5 to perform ambulatory functions with supervision of a specially trained companion in accordance with the user assessment and training certification program. The device is also intended to enable individuals with spinal cord injury at levels T4 to T6 to perform ambulatory functions in rehabilitation institutions in accordance with the user assessment and training certification program. The ReWalk is not intended for sports or stair climbing.

The indications for use for the pediatric exoskeleton would be similar to the ReWalk device, but the target population would be expanded to include pediatric patients, especially those with cerebral palsy, spina bifida and spinal muscular atrophy. An example of indications for use for the P-LEGS device is as follows:

- The device orthotically fits to the lower-limbs and part of the upper body. The device is intended to enable individuals with spinal cord injuries at levels (T7 to L5) and individuals with cerebral palsy, spina bifida and spinal muscular atrophy to perform ambulatory functions with supervision of a specially trained companion in accordance with the user assessment and training certification program. The device is not intended for sports or stair climbing.

New indications for use are cleared through the 510(k) notification whereas new intended use is granted/approved through a De Novo application or premarket approval and while the technological characteristics of the device may not be the entry point for new risks, the expansion of the target population to include children and those with cerebral palsy, spina bifida, spinal cord injury, spinal muscular atrophy or other conditions limiting independent mobility could be seen as potentially increasing the risk of device use due to the physical and psychological challenges that may be associated with these conditions.

IV. FDA REGULATORY CONTROLS

Federal law (Federal Food, Drug, and Cosmetic Act, section 513), established the risk-based device classification system for medical devices where each device is assigned to one of three regulatory classes: Class I, Class II or Class III, based

on the level of control necessary to provide reasonable assurance of its safety and effectiveness. For this and additional information on FDA regulatory controls see [28].

A. General Controls

General controls apply to all medical devices, unless exempted by regulations. If a device is exempted from one or more of the general controls, such exemptions are stated in the classification regulation for that device. General controls include provisions that relate to adulteration; misbranding; device registration and listing; premarket notification; banned devices; notification, including repair, replacement, or refund; records and reports; and good manufacturing practices.

B. Special Controls

Special controls are special regulatory requirements that FDA can apply to Class II devices – such as a requirement that the device must conform to a specific technical standard or undergo a specific type of testing or follow-up. FDA classifies into Class II devices for which general controls alone are insufficient to provide reasonable assurance of the safety and effectiveness of the device, and for which there is sufficient information that it would be possible to establish special controls to provide such assurance. In practice, FDA has applied special controls sparingly and many Class II devices come to market without special controls. Approximately 15% of all device types classified in Class II are subject to special controls [29]. The following list of special controls has been applied by the FDA to the class II devices of powered exoskeletons. Should the P-LEGS device be classified in the same or a similar manner then the similar controls would likely be applicable:

- Biocompatibility assessment
- Electrical, thermal, EMC, battery testing
- Software verification and validation and hazard analysis
- Design consistent with intended use
- Mechanical testing: Durability, simulated use, verification and validation

V. Additional Considerations in Pediatric Populations

In a guidance document titled, *Premarket Assessment of Pediatric Medical Devices* the FDA has sought to help define pediatric populations to increases standardization for medical devices. The subgroups and associated age ranges are listed in Table 2.

TABLE II. Pediatric Subgroups and Age Ranges

Pediatric Subgroup	Approximate Age Range
Newborn (neonate)	from birth to 1 month
Infant	greater than 1 month to 2 years
Child	greater than 2 to 12 years
Adolescent	greater than 12 to 21 years

The FDA has also sought to clarify the types of information needed to provide assurance of safety and effectiveness for pediatric devices and to provide guidance for clinical trial sponsors to assist in the overall protection of this more vulnerable clinical population. Certain considerations that apply to the pediatric population that would not factor into the design controls for adult devices is the likely duration of device use and its impact on the growth and the child's ability to reach important developmental milestones, as well as the natural progression of a condition and how these may impact physiological or psychological maturation of the child. An important set of questions for designers to consider is, will the child outgrow the device, and if so, at what rate and when is the required time for device adjustment/replacement? In regard to clinical trials, not only should the consent of the child's guardian be obtained, but assent of the child as well. The FDA has defined assent as a child's affirmative agreement to participate in a clinical investigation, and states further that mere failure to object may not be construed as assent. For these and additional considerations when developing a pediatric medical device see [30].

VI. Submission Pathway Evaluation

This section aims to provide information about the FDA pathways and discuss the applicability of each to the example device, P-LEGS.

A. Premarket Notification 510(k)

There are three types of Premarket Notification 510(k)s: The Traditional 510(k), the Special and the Abbreviated 510(k). For this example, the Traditional 510(k) pathway will be discussed. The Special pathway applies to a manufacturer who modifies its own legally marketed device and the design control procedures produce reliable results that can form part of the basis for substantial equivalence determination. The Abbreviated pathway may be chosen by device manufacturers when a submission relies on one or more of the following:

- FDA guidance document(s)
- Demonstration of compliance with special controls for the device type, either in a device-specific classification regulation or a special controls guidance document; and/or
- Voluntary consensus standard(s)

The key principle underlying the 510(k) pathway is the idea of substantial equivalence and the existence of a predicate device or devices. All 510(k) submissions must provide a comparison between the device to be marketed and the predicate device or devices. For a discussion on a possible predicate device for the P-LEGS exoskeleton see Section III (B).

The FDA has released a guidance document to assist medical device manufacturers in extrapolating clinical data from previous studies to support their submissions for pediatric devices. The hope is that this will potentially streamline the process for establishing a pediatric intended

use claim and enhance pediatric device development programs [31].

B. De Novo Pathway

Devices that are novel and thus unable to establish substantial equivalence to an already-marketed predicate device would be ineligible for the 510(k) pathway. However, such devices sometimes do not present a high degree of risk. When this is the case, it may be possible to pursue a de novo device classification in which the FDA determines the appropriate risk classification for the new device. Such classifications will typically (but not always) be to Class II.

The Food and Drug Administration Modernization Act of 1997 (FDAMA) added the De Novo classification option as an alternate pathway to classify novel medical devices that had automatically been placed in Class III after receiving a "not substantially equivalent" (NSE) determination in response to a premarket notification [510(k)] submission. Section 513(f)(2) of the FD&C Act was amended by section 607 of the Food and Drug Administration Safety and Innovation Act (FDASIA), on July 9, 2012, to allow a sponsor to submit a De Novo classification request to the FDA directly without first being required to go through the steps of submitting a 510(k) and having it be rejected as not substantially equivalent.

There are two options for De Novo classification for novel devices of low to moderate risk.

Option 1: Any person who receives an NSE determination in response to a 510(k) submission may, within 30 days of receipt of the NSE determination, submit a De Novo request for the FDA to make a risk-based evaluation for classification of the device into Class I or II.

Option 2: Any person who determines that there is no legally marketed device upon which to base a determination of substantial equivalence may submit a De Novo request for the FDA to make a risk-based classification of the device into Class I or II, without first submitting a 510(k) and receiving an NSE determination. Devices that are classified through the *de novo* process may be marketed and used as predicates for future 510(k) submissions [32].

In the event the device is not found to be substantially equivalent (SE) to the predicate device listed in the 510(k) section of the submission document, the De Novo pathway will likely be the alternative option. The De Novo pathway provides a path to market for devices of low to moderate risk but have been classified in class III due to not being SE to a predicate device.

C. Humanitarian Device Exemption pathway

This pathway was created in 1990 when Congress included a provision in the Safe Medical Devices Act in order to allow a pathway devoted specifically to Class III devices intended to treat diseases or conditions that affect small populations. This pathway allows a market application for a Humanitarian Use Device (HUD). A HUD is defined by the FDA as a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year [33].

If, in the P-LEGS submission application the target population was restricted to spinal cord injury in children, which is estimated to occur with a frequency of approximately 1,450 annually in the U.S. [34] then the population statistics would be within the pathway requirements, however if the FDA has reason to doubt that the device will be limited to the listed population then the application can be rejected. In the case of P-LEGS, the target populations have been listed and cerebral palsy alone occurs in 2-3 per 1,000 live births in the U.S. annually accounting for approximately 16,000 children per year. This would disqualify the device from being approved via the HDE pathway.

D. Premarket Approval (PMA)

The PMA approval pathway is the most stringent regulatory pathway and is generally applicable to novel and high-risk devices. It has the strictest controls and requires significant data and clinical testing. If regulators are unable to rely on general or special controls, the device may be classified as class III. None of the powered exoskeletons or powered rehabilitation devices with similar indications for use as the pediatric exoskeleton that are currently cleared by the FDA are classified as class III devices.

VII. Brain Computer/Machine Interfaces for Pediatric Rehabilitation

EEG-based BCI/BMI control of powered lower-limb robotics has been proposed for the assistance, restoration and rehabilitation of gait [35], but the majority of research to date has been in the adult population [3]. In addition to the use of these systems to infer the user's movement intent to control/command robotic exoskeletons, this tool could be used to investigate the effects that conditions such as cerebral palsy and pediatric spinal cord injury have on the developing brain and how rehabilitation therapies can be modified and personalized to meet the specific needs of each child.

Recent attempts to use BCI/BMIs in the pediatric populations have showed encouraging results. Qian Et al. used an EEG-based BMI training game for children with attention deficit/hyperactivity disorder (ADHD) and found that after an eight-week intervention period the training facilitated behavioral improvements by reorganizing functional networks in the brain [36]. Zhang et al. conducted a feasibility study to investigate the ability of school-aged children with no neuromuscular or developmental disabilities to use a BMI to control a remote car and a computer cursor and reported that the children were quickly able to achieve control and execute multiple tasks using the simple EEG-based BMI system. They also reported that higher performances were observed in older children. The mean age of children in the study was 13.2 ± 3.6 years [37].

Figure 7. Young boy wearing a prototype of a pediatric exoskeleton BMI system. Photo Credit: 160over90.

As part of the process of developing a BMI platform to investigate the developing brain and the longitudinal effects robotic assisted gait therapy can have on children with cerebral palsy, spinal cord injury and other conditions affecting their ability to walk, we have developed the lower limb pediatric exoskeleton (P-LEGS). Figure 7 shows a young boy wearing an EEG-based BMI system and a prototype of the P-LEGS exoskeleton device [38].

Early-feasibility testing to decode gait kinematics from able-bodied children during walking tasks has been performed [6] with promising results, but much work remains to be done to develop reliable BMI-exoskeleton systems that can be used to improve clinical outcomes for children with various conditions affecting their everyday functional abilities.

VIII. Conclusion

This overview of the FDA medical device regulatory pathways used an example of a pediatric lower-limb rehabilitation device (P-LEGS) to provide insight for device developers into important decisions when preparing to take a device to market in the United States. Important considerations when designing for pediatric populations are provided as well as ethical considerations when conducting clinical trials to collect data to support a submission application. Brain-machine interfaces for children hold promise for improving clinical outcomes for those with conditions such as cerebral palsy and spinal cord injury. Future work to develop reliable BMI-robot systems that can increase the clinical outcomes of gait rehabilitation for children is greatly encouraged. There is a need for pediatric specific medical devices that can incorporate design aspects to assist children not only in treating target conditions, but also in promoting and achieving developmental and growth milestones on the way to living an independent and rewarding life.

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References

[1] Contreras-Vidal J L *et al* 2016 Powered exoskeletons for bipedal locomotion after spinal cord injury *J. Neural Eng.* **13** 31001

[2] Young A, Ferris D. State-of-the-art and Future Directions for Robotic Lower Limb Exoskeletons. IEEE Trans Neural Syst Rehabil Eng. 2016; PP:1–1

[3] He Y, Eguren D, Azorín J M, Grossman R G, Luu T P and Contreras-Vidal J L 2018 Brain–machine interfaces for controlling lower-limb powered robotic systems *J. Neural Eng.* **15** 021004

[4] D. Eguren, M. Cestari, T. P. Luu, A. Kilicarslan, A. Steele and J. L. Contreras-Vidal, "Design of a customizable, modular pediatric exoskeleton for rehabilitation and mobility," 2019 IEEE International Conference on Systems, Man and Cybernetics (SMC), Bari, Italy, 2019, pp. 2411-2416.

[5] T. P. Luu, D. Eguren and J. L. Contreras-Vidal, "Control architecture and network communication for a pediatric exoskeleton," 2017 International Symposium on Wearable Robotics and Rehabilitation (WeRob), Houston, TX, 2017, pp. 1-1, doi: 10.1109/WEROB.2017.8383870.

[6] T. P. Luu, D. Eguren, M. Cestari and J. L. Contreras-Vidal, "EEG-based Neural Decoding of Gait in Developing Children," *2019 IEEE International Conference on Systems, Man and Cybernetics (SMC)*, Bari, Italy, 2019, pp. 3608-3612. doi: 10.1109/SMC.2019.8914380

[7] Flores MB, Da Silva CP. Trunk control and gross motor outcomes after body weight supported treadmill training in young children with severe cerebral palsy: A non-experimental case series. *Dev Neurorehab,* 2018;22(7):499-503, DOI: 10.1080/17518423.2018.1527862.

[8] Darragh AR, Huddleston W, King P. Work-related musculoskeletal injuries and disorders among occupational and physical therapists. American Journal of Occupational Therapy. 2009; 63(3):351–362.

[9] J. Hidler and R. Sainburg, Role of Robotics in Neurorehabilitation. Topics in Spinal Cord Injury Rehabilitation, vol. 17, pp. 42-49, 2011.

[10] Meyer-Heim A, Borggräfe I, Ammann-Reiffer C, et al.: Feasibility of robotic-assisted locomotor training in children with central gait impairment. Dev Med Child Neurol 49:900-906, 2007

[11] Meyer-Heim A, Ammann-Reiffer C, Schmartz A, et al.: Improvement of walking abilities after robotic-assisted locomotion training in children with cerebral palsy. Arch Dis Child 94:615-620, 2009

[12] H. I. Krebs et al., "Pediatric anklebot", Proc. IEEE Int. Conf. Rehabil. Robot., pp. 1-5, Jun./Jul. 2011.

[13] Borggraefe I, Schaefer JS, Klaiber M, et al.: Robotic-assisted treadmill therapy improves walking and standing performance in children and adolescents with cerebral palsy. Eur J Paediatr Neurol 14:496-502, 2010

[14] Smania N, Bonetti P, Gandolfi M., et al.: Improved gait after repetitive locomotor training in children with cerebral palsy. Am J Phys Med Rehabil 90:137-149, 2011

[15] Lerner ZF, et al.: An Untethered Ankle Exoskeleton Improves Walking Economy in a Pilot Study of Individuals With Cerebral Palsy. IEEE Trans Neural Syst Rehabil Eng. 2018 Oct; 26 (10):1985-1993.

[16] Lerner, ZF, Damiano, D. L. & Bulea, T. C. A lower-extremity exoskeleton improves knee extension in children with crouch gait from cerebral palsy. Science Translational Medicine 9, eaam9145 (2017).

[17] Dodd, K.J., Foley, S.: Partial body-weight supported treadmill training can improve walking in children with cerebral palsy: a clinical controlled trial. Dev. Med. Child Neurol. 49, 101–105 (2007)

[18] M. Willerslev-Olsen, T. H. Petersen, S. F. Farmer and J. B. Nielsen, "Gait training facilitates central drive to ankle dorsiflexors in children with cerebral palsy," Brain, A Journal of Neurology, vol. 138, no. 3, pp. 589-603, 2015
[19] https://rewalk.com/rewalk-personal-3/
[20] http://www.indego.com/indego/en/home
[21] https://eksobionics.com/
[22] https://www.cyberdyne.jp/english/products/HAL/index.html
[23] https://www.hocoma.com/us/solutions/pediatric/
[24] van Hedel, Hubertus J A et al. "Advanced Robotic Therapy Integrated Centers (ARTIC): an international collaboration facilitating the application of rehabilitation technologies." *Journal of neuroengineering and rehabilitation* vol. 15,1 30. 6 Apr. 2018, doi:10.1186/s12984-018-0366-y
[25] PCT/US2017/037457, *Customizable Orthotic/Prosthetic Braces and Lightweight Modular Exoskeleton*, filed December 11, 2018 under application number 16/308,964.
[26] https://www.fda.gov/media/90419/download
[27] https://www.fda.gov/medical-devices/premarket-notification-510k/how-find-and-effectively-use-predicate-devices
[28] https://www.fda.gov/medical-devices/overview-device-regulation/regulatory-controls
[29] Institute of Medicine, et al. *Medical Devices and the Public's Health: The FDA 510(k) Clearance Process at 35 Years*. 1st ed., National Academies Press, 2011.
[30] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/premarket-assessment-pediatric-medical-devices
[31] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/leveraging-existing-clinical-data-extrapolation-pediatric-uses-medical-devices
[32] https://www.fda.gov/about-fda/cdrh-transparency/evaluation-automatic-class-iii-designation-de-novo-summaries
[33] Halt, Gerald, et al. *FDA and Intellectual Property Strategies for Medical Device Technologies*. 1st ed. 2019, Springer, 2019.
[34] Parent S, Mac-Thiong JM, Roy-Beaudry M, Sosa JF, Labelle H. *Spinal cord injury in the pediatric population: A systematic review of the literature*. J Neurotrauma. 2011.
[35] Contreras-Vidal J L, Kilicarslan A, Huang H H and Grossman R G 2015 Human-centered design of wearable neuroprostheses and exoskeletons Ai Mag. 36 12–23
[36] Qian, X., Loo, B.R.Y., Castellanos, F.X. *et al.* Brain-computer-interface-based intervention re-normalizes brain functional network topology in children with attention deficit/hyperactivity disorder. *Transl Psychiatry* **8,** 149 (2018) doi:10.1038/s41398-018-0213-8
[37] Zhang J, Jadavji Z, Zewdie E, Kirton A. Evaluating If Children Can Use Simple Brain Computer Interfaces. *Front Hum Neurosci*. 2019;13:24. Published 2019 Feb 4. doi:10.3389/fnhum.2019.00024
[38] https://www.nature.com/articles/d41586-018-02478-0

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