PATIENT MONITORING AND CLINICAL TRIAL CONSIDERATIONS FOR THE DEVELOPMENT OF EXTRACLINICAL NEUROSTIMULATION THERAPY FOR PEDIATRIC ADHD

A Thesis

by

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ABSTRACT

Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric disorder characterized by a repeated pattern of inattention, hyperactivity, and impulsivity that pervades and inhibits daily life functions. ADHD is most commonly clinically managed using pharmacotherapy, but in pediatric ADHD populations, the use of stimulant medications is somewhat undesirable because of their high cost, impermanence, and numerous side effects. Neurostimulation is an emerging therapeutic alternative to pharmacotherapy, but the commercialization of a neurostimulation device for pediatric ADHD must consider how electrodes should be held near the head for a period of time in the order of hours. The prescription, distribution, and usage of a pediatric ADHD neurostimulation device must be carefully considered in the context of the patient, a child with a unique combination of inattention, hyperactivity, and impulsivity.

This work strived to analyze the distinct pain points present in the pediatric ADHD treatment market through stakeholder engagement, to develop an adherence monitoring system using the internet of things, to propose a pilot clinical trial protocol, and to create a model and run fabricated data. Overall, the stakeholder engagement process revealed a significant pain point in the remote monitoring of ADHD therapeutics, which informed the development of an IoT-based adherence monitoring system. This system was designed to collect the elapsed time of a treatment session and transmit that data to the cloud via Bluetooth® Low Energy (BLE) and a mobile device. Finally, a clinical trial protocol was developed to determine the potential effects of color and color choice as influencing

factors on pediatric ADHD patient therapeutic adherence rates. Three distinct models were developed and used to analyze fabricated data sets. These models were then used to draw conclusions about future work regarding pediatric ADHD therapeutic devices.

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Contributors

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NOMENCLATURE

ADHD	Attention deficit hyperactivity disorder
ADHD-IA	Attention deficit hyperactivity disorder, inattentive subtype
ADHD-HI	Attention deficit hyperactivity disorder, hyperactive-impulsive subtype
BLE	Bluetooth® Low Energy
CMS	Cerebro monitoring system
COVID-19	Coronavirus disease of 2019
HCRF	Texas A&M Human Clinical Research Facility
HIPAA	Health Insurance Portability and Accountability Act
I-Corps	Innovation-Corps
IMU	Inertial measurement unit
iOS	iPhone operating system
IoT	Internet of Things
IRB	Institutional review board
LIDAR	Light detection and ranging
MPR	Medication possession ratio
NSF	National Science Foundation
ODD	Oppositional defiant disorder
PDC	Proportion of days covered
PHI	Protected health information
ToF	Time-of-flight

TABLE OF CONTENTS

Page

LIST OF FIGURES

Page

LIST OF TABLES

Page

CHAPTER I

INTRODUCTION

Introduction of Work

Pediatric and adolescent patients with attention deficit hyperactivity disorder (ADHD) have unique needs when it comes to their healthcare. Generally, children and adolescents are concerned with the aesthetics of their medical devices, as they develop a sense of self, learn independence, and grow more concerned with socialization and peer relationships [1]. In particular, children and adolescents with ADHD have a unique set of needs when it comes to medical devices, as they are more likely to have difficulty remembering and staying attentive to therapy [2]. A device's aesthetic impression affects the consistency with which pediatric patients use the device. Therefore, there is a need for research on how aesthetic impression may affect adherence to therapy in children and adolescents with ADHD.

The use of medical devices for the treatment of pediatric ADHD is an expanding sphere of research, with significant attention being paid to non-pharmacotherapeutic options for use in a home environment [3, 4]. Alongside the implementation of device-based therapies for children and adolescents with ADHD, this work synthesized research done regarding (1) adherence patterns to device-based treatments among pediatric patients, (2) adherence patterns to pharmaceutical treatments among pediatric ADHD patients, and (3) the effects of aesthetic impression on treatment adherence. In order to fully understand the pediatric ADHD treatment market and its stakeholders, customer

discovery techniques were applied to a variety of known stakeholders in the device-based treatment market of pediatric ADHD. Novel remote adherence monitoring technology was developed in response to the needs elucidated from the stakeholder investigation, hereafter referred to as the Cerebro Monitoring System (CMS). Finally, an observational clinical trial was designed and modeled for future work to examine the possible effects of color and color choice on pediatric ADHD patient adherence rate to treatment.

Introduction to Attention Deficit Hyperactivity Disorder

Attention deficit hyperactivity disorder (ADHD) is a neuropsychiatric disorder which manifests in a pattern of inattention and/or hyperactivity-impulsivity which interferes with daily life functions. The pathophysiology, clinical manifestations, diagnostic criteria, clinical management, and therapeutic innovations in ADHD will be discussed presently.

Pathophysiology and Clinical Manifestations

Neurologically, ADHD is known to be a highly heritable disorder with extensive literature showing genetics as the main causal influence for ADHD, although there has been little clarity as to the specific genes involved [5, 6]. Most recently, genome-wide significance has been shown for 304 genetic variants in 12 loci [7]. Adhesion G Protein-Coupled Receptor L3 (ADGRL3) (previously known as LPHN3) is a well-studied gene associated with ADHD in a large sample of children and adults [6]. ADGRL3 is known to moderate serotonin and dopamine release in the brain, and suppression of ADGRL3 has been shown to cause hyperactivity in mice and zebrafish [8-10]. Additional well-researched pathophysiological causes of ADHD include prenatal exposure to maternal

anticonvulsant drugs and childhood exposure to lead [11-13]. Both exposures affect a fetus' or child's neurodevelopmental processes, alter a fetus' or child's neurological pathways, and can lead to the development of ADHD [13, 14].

The clearest functional picture of the pathophysiology of ADHD is perhaps the consideration of ADHD as an executive function disorder [15, 16]. Executive functions are neurocognitive processes that involve developing a problem-solving strategy to attain a future goal [17, 18]. These processes are thought to require multiple neural networks involving the thalamus, basal ganglia, and prefrontal cortex [17, 19]. In ADHD, the executive functions of response inhibition, vigilance, spatial working memory, and planning are most commonly inhibited [17, 18]. There are three main identified abnormalities in the brains of patients with ADHD – firstly, the connection between the prefrontal cortex and the dorsal neostriatum; secondly, the connection between the basal ganglia and the dorsomedial thalamus; and thirdly, the connection between the thalamus to the prefrontal cortex [15, 20]. These abnormal connections interrupt executive functions and therefore result in the functional symptoms of ADHD [16]. Functional and structural imaging of the brains of patients with ADHD has shown abnormalities in specific connections related to dopamine release and the prefrontal cortex [15, 20]. An understanding of the associated executive function impairment is a vital part of understanding ADHD as a whole.

ADHD is identified to have three subtypes – predominantly inattentive (IA), predominantly hyperactive-impulsive (HI), and a combined type, which is most common [21]. Predominantly inattentive ADHD (formerly known as attention deficit disorder or

ADD) is marked by difficulty maintaining focus or paying attention to detail [2]. Predominantly hyperactive-impulsive ADHD (traditionally known as ADHD) is marked by restlessness, fidgeting, and interruption of others [2]. Combined-type ADHD is marked by a combination of the above symptoms that varies by patient but maintains a general convergence on difficulty with impulsiveness, hyperactivity, and inattention [2]. More specific diagnostic criteria per subtype will be discussed subsequently.

ADHD manifests in unique ways for pediatric and early adolescent patients throughout their academic, social, and home settings [2]. In an academic setting, symptoms of ADHD-IA could include constantly failing to remember one's backpack, forgetting tasks, overlooking details in assignments, daydreaming, and poor organizational skills. Symptoms of ADHD-HI in an academic setting could include difficulty sitting still and following classroom etiquette, excessive talking or interrupting the teacher, and overall restlessness. In social settings, a patient's inattention, hyperactivity, and impulsiveness can result in difficulty following social cues and norms and therefore facing hardship when forming friendships.

Among ADHD patients, there are a number of notable common comorbidities, including other psychiatric disorders, learning disabilities, and oppositional defiant disorder (ODD) [22-25]. The difficulty with social situations alongside difficulty with emotional regulation in children with ADHD can be associated with anxiety and/or depression [23, 25, 26]. Recent literature speculates that the association between ADHD and other psychiatric disorders may be genetic, as there is some evidence of coordination among patients with ADHD in several genetic loci previously associated with depression

and schizophrenia [7, 27-29]. There is additional literature showing coordination among patients with ADHD in a genetic locus regulating speech and learning [7, 30]. Oppositional defiant disorder is a highly significant comorbidity to ADHD, occurring in large numbers among ADHD patients and warranting strong consideration when gaining understanding of a typical pediatric population with ADHD [26, 31]. Identification and understanding of the behavior patterns of children with ADHD is vital to the pursuit of possible treatment options and accommodations.

Diagnosis

ADHD is most commonly diagnosed in children and young adults, with approximately 8% of children having been diagnosed with ADHD [32]. In the United States, the most common diagnostic system is the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), published by the American Psychiatric Association [2]. Testing based on the DSM-5 criteria is commonly done via behavior rating scales, which are filled out by the patient and various individuals who know the patient, and then interpreted by a clinician. One such rating scale is the ADHD-RS-V, which is an 18-part questionnaire that includes questions about specific ADHD-IA and ADHD-HI symptoms completed by the patient, the patient's parent, and the patient's schoolteacher [33]. The ADHD-RS-V requires that at least 6 symptoms be present for at least 6 months before diagnosis, in coordination with the DSM-5 criteria [2, 34, 35].

Despite the simplicity of behavior rating scales, there is much controversy surrounding their use. Malingering, the intentional exaggeration of psychiatric symptoms or behaviors, is rampant in ADHD testing. Patient malingering is notable in pediatric

populations but more common in adolescent and adult populations, due to the lucrative nature of illicit use of stimulant therapies and an overall awareness of the accommodations that an ADHD diagnosis can provide [36-41]. Behavior rating scales are inherently subjective and therefore there is great interest in the development of robust electroencephalography (EEG) diagnostics for ADHD [42, 43]. In 2013, the FDA approved the Neuropsychiatric EEG-Based Assessment Aid (NEBA) system to be used as a supplemental tool for ADHD diagnosis and treatment planning alongside the guidance of a clinician [42-45]. EEG data vary widely among ADHD patients, by individual and by subtype, which is why EEG is unable to form a declarative diagnosis on its own [42, 45-47].

Clinical Management and Therapeutic Interventions

The standard of care for pediatric ADHD varies with age and intensity of symptoms but is likely to include a combination of school accommodations, behavioral therapy, and medication. For very young patients and/or patients with less-inhibiting symptoms, behavioral therapy is likely to be considered first [48]. For older patients and/or patients with more-inhibiting symptoms, a combination of medication, behavioral therapy, and classroom accommodations is likely to be considered first [48]. Cognitive-behavioral therapy and behavioral parent training programs are proven therapeutic interventions shown to have positive effects in the treatment of ADHD and ODD, among other comorbidities [49-52]. School accommodations vary by child, school, and schoolteacher, but children with ADHD who meet the necessary criteria are entitled to accommodations through Individuals with Disabilities Education Act (IDEA) and Section 504 of the

Rehabilitation Act ("Section 504") [53, 54]. Stimulant medications are the primary form of pharmacotherapy for children with ADHD, despite the considerable side effects experienced by most patients [48, 55]. The most researched stimulant medications are methylphenidate and amphetamine, which both focus attention and improve executive function through increased release of norepinephrine and dopamine in the prefrontal cortex [56]. Most stimulant medications exhibit a pharmacodynamic profile of a quick onset of therapeutic effects and short duration of action (varying from approximately 2-12 hours), and therefore must be taken any time focused attention and/or improved executive functioning is desired [57, 58].

Recent Innovations in Therapeutic Interventions

Recent developments in the neurological and psychological etiology of ADHD have led to increased innovation of new therapeutic interventions. The most notable innovation in pharmacotherapeutic treatment for ADHD is the development of Strattera (atomoxetine), a nonstimulant medication FDA-approved specifically for an ADHD indication [50, 59]. Strattera is a promising treatment option that has been proven to successfully ameliorate a number of ADHD symptoms in children and adults. Additionally, neurostimulation systems have begun to be developed for the treatment of ADHD in children. Neurostimulation is the purposeful modulation of the nervous system's activity using invasive (i.e., deep brain stimulating microelectrodes) or non-invasive (i.e., transcranial stimulation) methods. There are two main theories to explain the effects of neurostimulation – augmentation theory and electroceutical theory. Electroceutical treatment involves the potentiation of biochemicals using an applied electric field [60].

Neurostimulation, as explained by electroceutical theory, utilizes an applied electric field to increase or decrease the chemical potential of one or many biochemicals and therefore alter communication between specific nerve fibers to achieve therapeutic effects. The augmentation theory attains therapeutic effects through an applied electric field, which then causes change to transmembrane potentials, membrane permeability, or electroactivity of receptors or receptands [61, 62]. For the treatment of ADHD, transcranial direct current stimulation (tDCS) and trigeminal nerve stimulation (TNS) are promising interventions. Transcranial direct current stimulation has been shown to reduce clinical manifestations of ADHD and may be able to improve memory and attention performance, but is still in pilot studies and has not been approved by the FDA [63]. TNS can be achieved non-invasively, with external electrodes and an on-body pulse generator, or invasively, with subcutaneously implanted electrodes and an implantable pulse generator [63]. NeuroSigma was the first company to receive FDA clearance for a neurostimulation device with a pediatric ADHD indication, called the Monarch eTNS System® [64]. Neurostimulation offers pediatric ADHD patients a promising, powerful treatment option, which is sure to gain traction as the technology develops further.

Introduction to Pediatric ADHD Therapeutic Adherence Principles

Adherence to medical device use by pre-adolescent patients has been studied extensively in the existing literature, with much attention paid to the changing interpersonal relationships that children experience during this period of development [1,

65-76]. Important factors associated with strong adherence to treatment in children and adolescents have been shown to include the following:

- Active parental involvement in treatment [66-70, 72].
- Patient's own positive attitude toward treatment [65, 68, 70, 72].
- A sense of social normality and perceived social acceptance of treatment by peers [65, 68, 70, 71, 74].
- Patient's sense of control and ability to carry out treatment independently [68-71, 73].

The present work proposed the use of visual aesthetics to encourage adherence to treatment in children and adolescents. By offering patients a choice of color of their device, this work aimed to improve adherence by improving the patient's own positive attitude toward treatment, instill a sense of social normality and social acceptance by peers, and impart the patient with a sense of control and independence with regard to their medical treatment.

In addition to the special consideration that must be given for treatment of pediatric patients, appropriate consideration must be given for pediatric patients with attention deficit hyperactivity disorder (ADHD). Pediatric ADHD is a very well-studied syndromic disorder and is particularly well described in the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [2]. Children with ADHD exhibit various combinations of inattention, hyperactivity, and/or impulsivity consistently over time [2]. The symptoms of pediatric ADHD patients have a profound impact on their behavioral patterns in all aspects of daily life. More specifically, ADHD patient adherence

to various pharmacotherapies is quite poor and depends greatly on many factors outside a child's control [20, 77-80]. As novel treatments are developed for the treatment of ADHD, extensive consideration must be given toward the encouragement of adherence in the treatment population.

CHAPTER II

ADHD TREATMENT STAKEHOLDER INVESTIGATION

Introduction

The first aim of this body of work was to fully understand the pediatric ADHD treatment market, ensuring that any ensuing innovation will bring value to the current market. Qualitative analysis methods were applied to learn about the stakeholders and their pain points, and were based on the Lean LaunchPad® methodology outlined by the National Science Foundation (NSF) Innovation-Corps (I-Corps) [81, 82]. More specifically, this work aimed (1) to understand pain points of the current pediatric ADHD treatment options, (2) to identify the paying customer in the current pediatric ADHD treatment sphere, and (3) to learn about how neurostimulation devices might be marketed and sold for the treatment of pediatric ADHD. The use of thematic analysis of the transcribed semi-structured interviews enabled actionable conclusions to be drawn by question and by section, to elicit the most pertinent themes regarding ADHD treatment in children and the general perception of a device-based treatment regimen.

Materials and Methods

Identification of Stakeholders

Identified stakeholders in the pediatric ADHD treatment market included parents of children with ADHD, ADHD patients, schoolteachers, school nurses, pediatric healthcare providers, and psychiatric healthcare providers. These stakeholders form a

complex web of interested parties in the adherence of children with ADHD to their prescribed treatment regimen. A preliminary, original list of stakeholders was composed of various individuals within 50 miles of the Bryan College Station area. This list was later expanded to include individuals across Texas, when COVID-19 social distancing guidelines required all interviews to become virtual interviews. As the interviews were conducted, referrals were requested and followed up to grow the list of stakeholders and obtain a more complete understanding of the treatment environment.

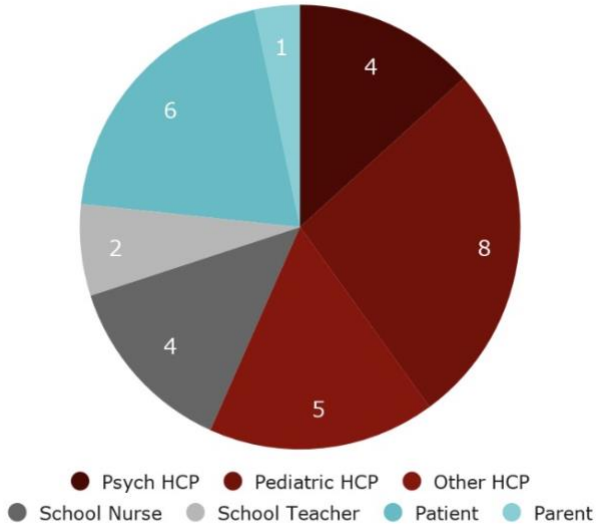
Interview Methodology

A series of questions was formulated for the semi-structured interviews, with three groups of questions exploring the problem, solutions, pricing, and possible go-to-market strategies (Appendix A). The same questionnaire (Appendix A) was used for all interviewed stakeholders to enable more rigorous analysis. Thirty stakeholders were contacted and scheduled for a ~15-minute interview, via video chat or via phone, in compliance with Texas A&M University, local, and national COVID-19 social distancing guidelines. The list of questions was sent to interviewees in advance via e-mail and most of the interviews were recorded for transcription, given the consent of the interviewee. If consent was not granted by the interviewee for recording, the interviewer took detailed notes of the conversation and question responses. Responses were recorded in an Excel spreadsheet by the interviewer after the conclusion of the interview.

Results and Discussion

The stakeholders' answers were recorded and analyzed using thematic analysis per question to distill the interview transcripts into themes, roughly sorted by section. This work includes answers from thirty total individuals – four psychiatric healthcare providers, eight pediatric healthcare providers, five other healthcare providers, four school nurses, two schoolteachers, six patients, and one parent of four patients, as shown in Figure 1.

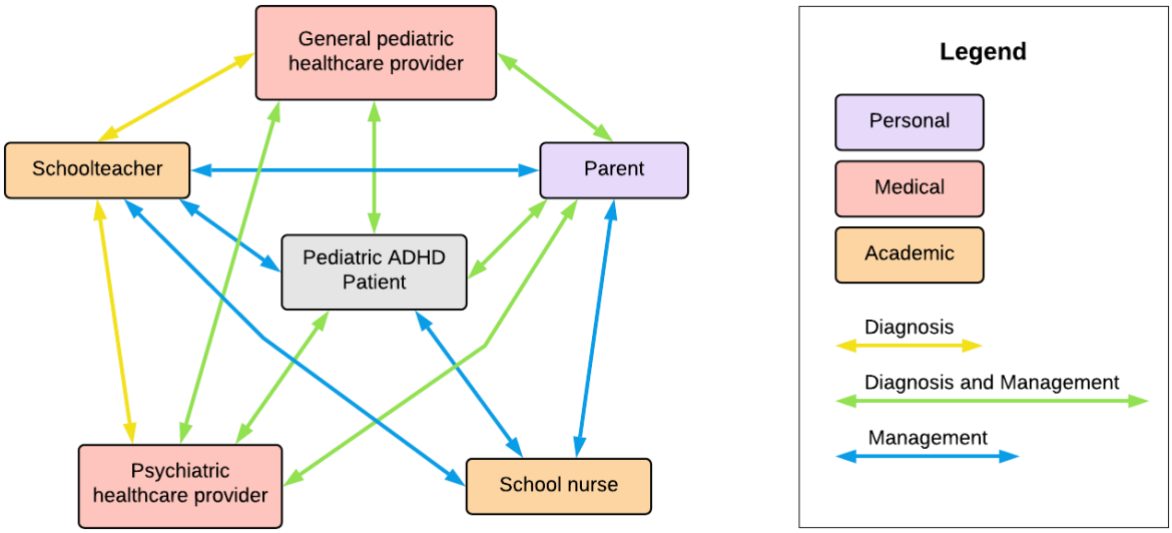
Figure 1. Composition of interviewed stakeholder group.



Stakeholder Environment and Relationships

The information gained from these interviews revealed a complex web of interactions between general pediatric healthcare providers, psychiatric healthcare providers, schoolteachers, school nurses, parents of patients, and pediatric patients, as shown in Figure 2.

Figure 2. Pediatric ADHD treatment stakeholder environment, involvements, and interactions.



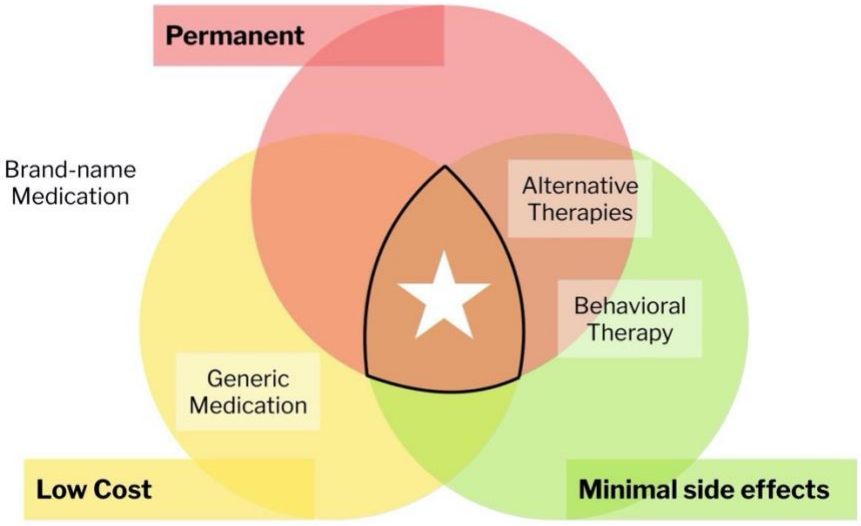
Each party plays a specific role in the diagnosis and management of pediatric ADHD, often interacting with one another and influencing each other's actions. Generally speaking, a diagnosis is made upon self-reporting to either a general pediatric healthcare provider or a psychiatric healthcare provider by the patient, their parent(s), and their schoolteacher, as discussed in Chapter I. Once a diagnosis is made, the patient is clinically managed by their parent(s), healthcare provider(s), and sometimes, the school nurse. Some patients are diagnosed and managed exclusively by a general pediatric healthcare provider, some exclusively by a psychiatric healthcare provider, and some are diagnosed and managed concomitantly by a general pediatric healthcare provider and a psychiatric healthcare provider. This largely depends on the comfort level of the general pediatric healthcare provider with pediatric psychiatry and the presence of possible comorbidities that may complicate the process and be better handled by a psychiatric professional. The

healthcare providers involved with a specific patient are responsible for clinical management and the administration of pharmacotherapy. The schoolteacher is responsible for the patient's behavioral management in the classroom. If the patient is on immediate-release stimulant pharmacotherapy, the schoolteacher is also generally the first to know if the patient missed a dose on a specific day, as their behavior will be affected when the child arrives at school. This is where the school nurse's responsibilities become apparent- to administer medication for patients requiring mid-day dosing and to manage side effects that occur during school hours. Finally, the parent(s) of a pediatric patient with ADHD are largely responsible for all the activities surrounding treatment, as they advocate for and represent their child throughout the process. All of these parties must be in regular communication with one another to ensure optimal diagnosis and clinical management of a pediatric ADHD patient.

Key Findings

The most common current treatment options include pharmacotherapy, behavioral therapy, and alternative therapies, as discussed in Chapter I. Through the customer discovery process, there were three desirable features of a "perfect" ADHD treatment solution – low cost, permanence, and minimal side effects. Each of the common treatment options addresses some of these desirable features, but none addresses all three, as shown in Figure 3. A distinction is drawn between generic and brand-name medication options because of the drastic difference in cost to the patient, which will be discussed subsequently, in the Purchase Options section.

Figure 3. Desirable features of ADHD treatment and current treatment options.



Brand-name medication is not permanent nor low-cost and has significant side effects. Generic medication is low-cost but is also not permanent and has significant side effects. Behavioral therapies have minimal side effects, can be permanent but is generally not, and can be quite high cost to patients. Alternative therapies can claim to be more permanent with less side effects but are very high cost and generally not well-proven as effective in the literature. Alternative therapies discussed in this work include hyperbaric oxygen therapy and neurofeedback therapy. Despite its lack of the key desirable features identified above, stimulant medication is the most prominent and popular treatment option discussed in these stakeholder interviews. Thus, the ensuing discussion will be focused mainly on stimulant pharmacotherapy for the management of pediatric ADHD.

Problem

This work identified three key barriers to access of ADHD treatment options – fear of misuse, cost, and social stigma. Healthcare providers and parents alike are often

concerned about possible misuse of stimulant medication, given that most are Schedule II controlled substances [83]. Because of this classification, healthcare providers, under normal circumstances, cannot prescribe more than 30 days' medication at a time and must follow-up with each patient approximately once per month [84]. This research perceived a significant fear of misuse in prescribing physicians and parents alike. Another identified barrier to access of stimulant medications is cost. Depending on which type of medication is prescribed and is found to work well for the patient, the cost of monthly medication can be steep. This can be ameliorated by seeking insurance coverage for a specific stimulant medication or circumvented altogether by finding an alternative medication option that is already covered by the patient's insurance. One general pediatric healthcare provider stated that "it is hard to find a prescription and medication that is effective and helpful for the patient, while also being covered by insurance". An additional barrier to access of stimulant medications is the perceived social stigma surrounding stimulants. This theme was most prominent among interviews with general pediatric healthcare providers, as several mentioned situations in which they felt a patient was a great candidate for stimulant medication, but the parents of the patient were extraordinarily hesitant to start their child on stimulants. One physician elaborated on the familial strife this can cause, that when parents hesitate to start their child on stimulants, it "creates frustration and difficulties for the patients themselves". Only one physician was able to pinpoint what exactly she felt was causing the social stigma, stating that it was "from fear that the stimulants could cause addiction problems later". There is substantial evidence in the literature showing no association between stimulant use and substance use disorder in patients with ADHD,

even when stimulant treatment is initiated in childhood [85-90]. More research must be done to further clarify the role of stimulant medication in substance use disorder's comorbidity with ADHD.

Four key barriers to adherence to stimulant treatment were identified during the customer discovery process – inherent ADHD traits, parental involvement, comorbidities such as oppositional defiant disorder (ODD), and difficulty swallowing pills. Patients with ADHD by definition are inattentive, hyperactive, and impulsive, and thus do not have favorable traits for adhering well to strict medication schedules. A patient's adherence to stimulant medication varies from patient to patient, of course, and was found to be highly dependent on the level of parental involvement that the patient experiences. The importance of parental involvement was mentioned 16 times throughout the interviews, most stating that "compliance [to medication] without parents is extremely low…with parents the number [adherence rate] is higher". One point made that is worth mentioning is that because of ADHD's highly heritable nature, the possibility of a parent of a patient having ADHD as well as their child is higher than average [5, 6]. Therefore, adherence to medication can be affected by not only the child's symptoms, but those of a parent as well. Comorbidities to ADHD were also frequently mentioned in the interviews, including obsessive-compulsive disorder (OCD), autism spectrum disorder, oppositional defiant disorder (ODD), and bipolar disorder. This matches what is found in the literature regarding common comorbidities with ADHD [91]. Specifically, ODD can create difficulty with adherence to treatment, as patients with ODD are inherently defiant of authority and argumentative [2]. Finally, the last key barrier to adherence identified in this

work is simple but notable – the difficulty that young children can have with swallowing pills. This was mentioned five times in the interviews, and often delays stimulant treatment to an older age when the patient can better tolerate oral medication.

There are also barriers to an effective and tolerable medication type and dosage. Patients and physicians expressed that finding the most effective medication and dosage for the patient's specific ADHD symptoms was extremely difficult. The most common strategy was simply "trial and error" with medications, in some cases taking several years before a suitable medication and dosage was found. The therapeutic window for most stimulants is quite narrow, with the optimal dosage being quite laborious to find for each patient and the increase in side effect severity occurring rapidly outside the therapeutic window. Stimulant side effects were the most mentioned topic in this study, with 43 mentions overall; specific side effects mentioned are listed in Table 1.

Table 1. Commonly reported side effects of stimulant medication.

Side Effect	**Number of times mentioned**
Weight loss and appetite changes	14 mentions
Mood swings and emotional lability	9 mentions
Difficulty sleeping, insomnia	7 mentions
Overall sadness, change in emotion	5 mentions
Nausea, upset stomach, "feeling sick"	4 mentions
Headache	4 mentions
Unintended hyperfocus	2 mentions

The side effects to stimulant medication can be quite harsh and can add significant complications to the management of ADHD, particularly in children. One adolescent patient stated:

> The side effects can really impact your life. I've been taking medication for years, since elementary [school]. I know in elementary [school], some people would ask me if I was mad at them because I was not as creative or expressive as before. The medicine sometimes doesn't make you feel like yourself.

This theme, of the stimulant medication causing a patient to not "feel like themselves" was echoed in many of the young adults with ADHD interviewed. They were quite sincere in their discussion about the side effects they experienced and discussed how impactful this feeling had been in their social and familial relationships.

Solution

In the *Solution* section of the customer discovery interviews, three desirable features were elucidated after a minimal introduction to neurostimulation devices – appeal to children, adherence monitoring, and evidence of effectiveness. Many stakeholders discussed the need for treatment to be appealing to children in some way to engage them in the treatment process. One schoolteacher stated this, on the importance she thought of appeal to children:

> It depends on how it is presented. Some kids do not even like glasses, [because] they want it to be seen as 'cool'. They [children with ADHD]

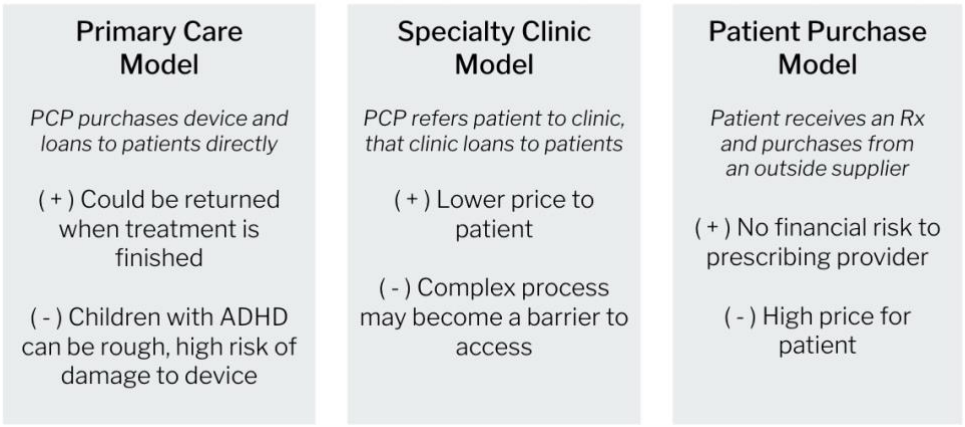
> would probably be more apt if they could wear it [a novel treatment device] with a hat. Kids are likely willing to try.

Two of the psychiatric healthcare providers echoed this sentiment, stating the vital need for some kind of emotional, creative, or imaginative appeal for children with ADHD to engage with the device. An additional feature requested by general pediatric healthcare providers and patients was that of remote adherence monitoring. Physicians reported appreciating the compliance estimate made available by looking at pharmacy refill requests and would like to see some data on patient usage for a treatment device in the home. Patients also stated that they would prefer their clinician "closely monitor my treatment and usage of the device". The third desirable feature of a possible ADHD neurostimulation device revealed in this study is a large body of evidence for effectiveness. This was mentioned 14 times across the interviews by general pediatric healthcare providers, patients, and parents. The physicians generally indicated that the device would need to be as effective as stimulant medication to prescribe it to their patients, and that reduced side effects would be a great benefit to increase prescription.

Purchase Options

In the Purchase Options section, interviewees were proposed three separate purchase models, as described in Figure 4.

Figure 4. Purchase option models proposed to stakeholders.

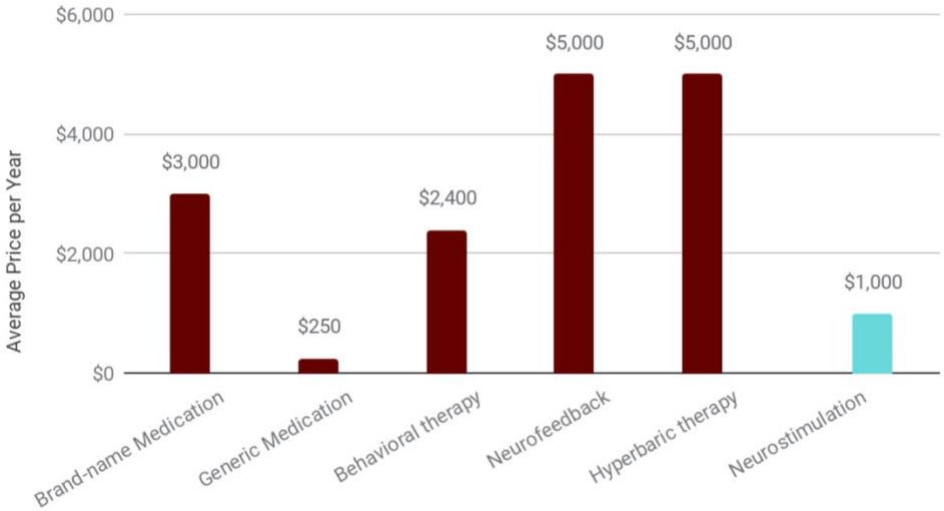


The primary care model shows that a primary care provider or general practice clinic purchases the device and then loans it out to its patients. The largest pro to this model is that the device could be returned when treatment is finished, likely reducing the cost of treatment for the patients. The largest con to this model is that children with ADHD are generally hyperactive and impulsive, thus increasing the risk of damage to the device while loaned out to the patient. This incurs difficulty on the part of the primary care physician, as the devices may quickly become damaged and/or unusable. The specialty clinic model shows that when a primary care provider identifies a patient as a good candidate for neurostimulation treatment, they refer that patient to an outside clinic, which manages the treatment course and loans devices out to patients. The most significant benefit of this model is that it could reduce the price of treatment to patients and remove some of the responsibility of implementing new technology from the primary care provider. The most significant disadvantage to this model is that the added step in the process may unnecessarily complicate the system and may become a barrier to access for patients. The patient purchase model shows that a patient receives a prescription for

neurostimulation treatment from their healthcare provider, and then purchases the device themselves from an outside supplier. The most compelling advantage to this model is that it requires no financial risk on the part of prescribing provider, increasing the likelihood of the device being prescribed overall. The most compelling disadvantage to this model is the high cost that is the full responsibility of the patient. Despite this point, the patient purchase model was the most popular among interviewed stakeholders because of the ease of accessibility to treatment and the low financial risk required from providers.

Interviewees reported their perception of the average price of various ADHD treatments with which they were familiar. These estimates were analyzed and distilled into five categories – brand-name medication, generic medication, behavioral therapy, neurofeedback, and hyperbaric therapy, shown in maroon in Figure 5. The interviewees were also asked to report approximately what price they thought was appropriate for one round of neurostimulation treatment for ADHD, shown in turquoise in Figure 5.

Figure 5. Reported average price per year of selected ADHD treatment modalities.



Identified Advantageous Entry Markets

Throughout the analysis of the stakeholder interviews, a few key advantageous entry markets were revealed. These highly specific entry markets have unique pain points that are neglected by current pediatric ADHD treatment modalities. These markets include multi-ADHD-child families, very young children with severe ADHD, families desiring conservative treatment modalities, patients requiring brand-name medication, and patients with contraindications to stimulants. Multi-ADHD-child families are somewhat common, due to the high heritability of ADHD. Over time, neurostimulation could prove to be a highly cost-effective option for families requiring pharmacotherapy for several children over many years. Very young children with severe ADHD would also be a key entry market, as they are often not able to swallow pills consistently yet virtually require clinical intervention in some form. Many stakeholders expressed the large population of families who feel a social stigma surrounding stimulant medication and generally desire more conservative treatment for their children. A neurostimulation device could offer them effective treatment without the use of stimulant medication. Patients who require brand-name medication would also be a key entry market, as brand-name stimulant medications carry extremely high costs to patients. The final key entry market identified in this study is patients for whom stimulant medication is contraindicated – patients with symptomatic cardiovascular disease, hyperthyroidism, hypertension, and/or a history of substance use disorder, among other things [92]. For these patients, there are currently very few options of any kind for long-term, effective management of ADHD. This is a primary entry market for neurostimulation devices for the treatment of pediatric ADHD.

Conclusion

A customer discovery process, as outlined by the National Science Foundation (NSF) Innovation-Corps (I-Corps), designed and executed for investigation of the pediatric ADHD treatment market. Thirty stakeholders were interviewed using semi-structured interview methodology, their responses recorded and analyzed for key themes and insights. A specific interest was paid to the developing technology of neurostimulation for the treatment of pediatric ADHD, and the stakeholders gave insightful feedback on problems in the pediatric ADHD treatment market, important features to be considered, and purchase option modeling for the distribution of neurostimulation devices throughout the market. This work informed additional research regarding the development of a remote adherence monitoring system for neurostimulation devices (Chapter III) and the implementation of aesthetically appealing features to neurostimulation devices (Chapter IV).

CHAPTER III

IOT METHOD FOR NEUROSTIMULATION MONITORING

Introduction

In Chapter II, three key desirable features of developing neurostimulation devices were elucidated from semi-structured interviews with stakeholders in the pediatric ADHD treatment market. These features include an appeal to children, adherence monitoring, and evidence of effectiveness. Providing strong evidence of the effectiveness of neurostimulation for the treatment of pediatric ADHD is outside the scope of this body of work. However, appeal to children and adherence monitoring informed the development of the Cerebro Monitoring System (CMS), to be discussed presently, and the clinical trial protocol design in Chapter IV.

The Cerebro Monitoring System (CMS) was developed as a solution to the problem of accurate measurement of a patient's adherence to neurostimulation treatment in an extraclinical environment, as identified in Chapter II. Adherence to pharmacotherapy can be measured either directly, through blood and urine assays or direct observation of treatment, or indirectly, through patient self-reporting, pill counters, or pharmacy refill claims [93, 94]. Few solutions have been developed for monitoring adherence to non-pharmacological, device-based treatments. Of these, most have been focused on asthma and cystic fibrosis patients, utilizing various methods to monitor adherence to inhalers and nebulizer treatments [95, 96]. These solutions do not properly adapt to a device worn on the head, as they rely on either emitted acoustic measurements or pre-programmed dosage

counters [96, 97]. Because the neurostimulation device of interest does not emit any detectable sound, acoustic-based monitoring techniques are not appropriate. Additionally, the neurostimulation device of interest does not include an expendable dose portion, such as a nebulizer does. Accelerometry has been used in a number of adherence monitoring systems, most notably in scoliosis brace treatment monitoring [98]. Systems such as these could possibly be adapted to a neurostimulation device for ADHD but are not readily, commercially available for use. Thus, a novel monitoring technique had to be developed that utilizes accelerometry and gyroscope measurements for the purposes of these experiments. The CMS was developed to meet the needs of this specific application but is able to be adapted for many other medical device adherence monitoring applications.

Materials and Methods

Internet of Things Approach

An internet of things (IoT) approach was used to enable remote adherence monitoring of pediatric neurostimulation patients. The internet of things, as applied in the medical field, will vastly increase the collection, transmission, reception, and analysis of patient data [99]. Bluetooth Low Energy (BLE) was chosen for communication for this application because of its low power consumption requirements, reliability, and compatibility with commercially available mobile devices, such as the iPhone. BLE requires the use of two types of devices – central device and peripheral devices [100]. Central devices scan the surrounding area for peripheral devices to read, while peripheral devices advertise information to be read by central devices. Many commercially available

mobile devices can act as both central and peripheral devices. For this application, the mobile device acts exclusively as a central BLE device, while the Arduino board acts exclusively as a peripheral BLE device. In order to advertise its information, a peripheral device creates and broadcasts packets known as services, a collection of characteristics [100]. A connection is initiated by the central BLE device, which then reads the services advertised by the peripheral BLE device. Use of the BLE method drastically reduces the power consumption of the peripheral BLE device over time because when not in connection with the central device, the peripheral does very little except maintain its service advertisement. Once a connection is established, one device takes on the role of the GATT server and the other takes on the role of the GATT client [100]. In this application, the device hardware becomes the GATT server, sending information to the GATT client, the mobile device. This data is received through use of a commercially available iOS app, the LightBlue® app by Punch Through, Inc. The LightBlue® app is designed for straightforward BLE prototyping and experimentation [101]. The LightBlue® app enables a mobile device to scan for and connect to peripheral BLE devices in the nearby vicinity, accept data from the peripheral device, and then send that data to the cloud via Adafruit IO [101]. The data is then stored with Adafruit IO for future retrieval [102].

Hardware Components

The Cerebro Monitoring System (CMS) is designed to collect elapsed time of wear of each prototype by each patient. Each CMS consists of a time-of-flight sensor, an Arduino Nano 33 IoT board, and a battery holder. Each time-of-flight sensor (“ToF

sensor") was purchased from Adafruit Industries (Adafruit VL6180X), which utilizes a light detection and ranging (LIDAR) sensor to detect objects between 5 and 100 mm away [103]. Each Arduino Nano 33 IoT ("Arduino board") was purchased from Arduino AG™. Each Arduino board contains an on-board LSM6DS3 inertial measurement unit (IMU) with 3D gyroscope and 3D accelerometry capabilities and enables Bluetooth® low energy (BLE) communication [104, 105]. Both the ToF sensor and the Arduino board components utilize I2C for communication [103, 106]. Figure 6 shows how the components were assembled to collect and send time of flight, gyroscope, and accelerometry data. Figure 7 is a set of photographs of the ToF sensor soldered in connection to the Arduino board.

Figure 6. Schematic illustration of the assembled ToF sensor and Arduino board.

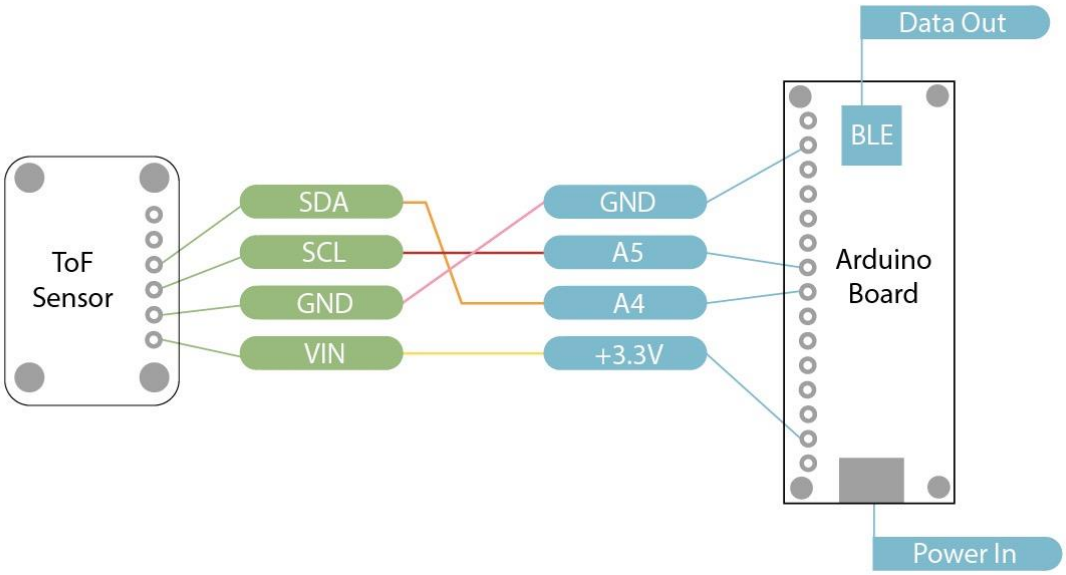
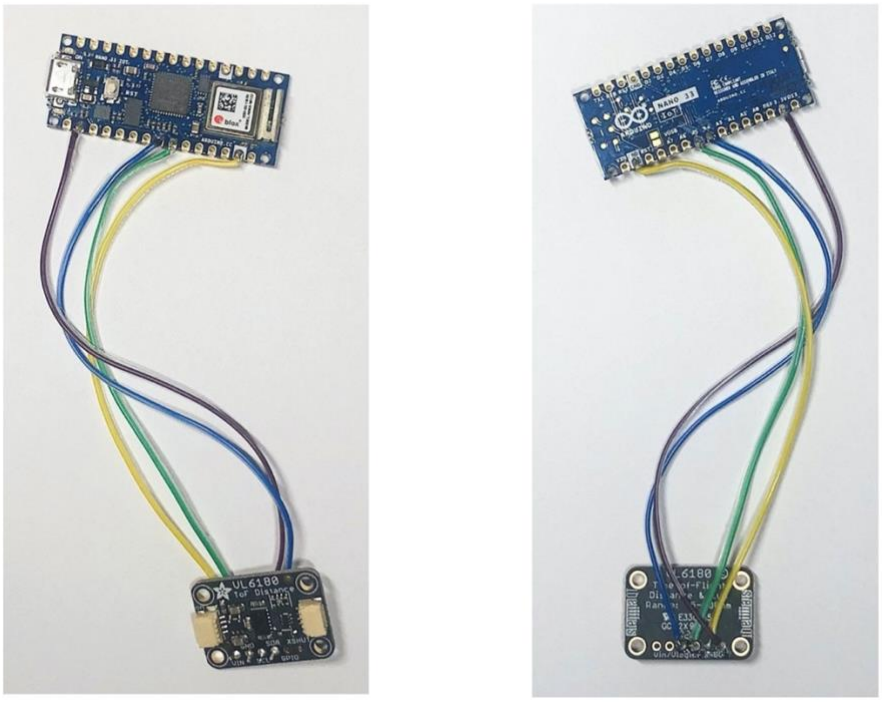


Figure 7. Front and back photographs of the ToF sensor and the Arduino board wiring.



Fabrication Approach

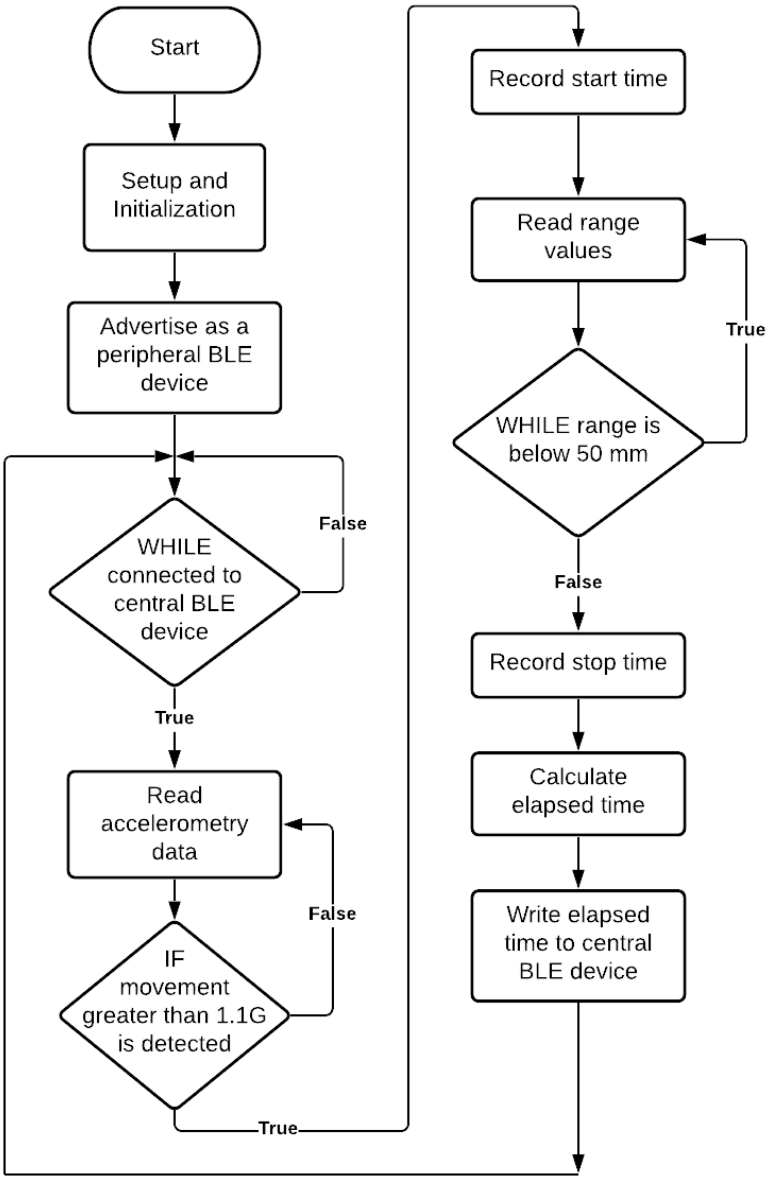
The device is powered via a micro-USB port on the Arduino board, as shown in Figure 6. Micro-USB battery holders containing three AA batteries were attached inside the beanie fold and used to power the CMS. All the hardware (the battery holder, Arduino board, and ToF sensor) are held securely inside the beanie fold. A small opening was cut inside the beanie to allow the ToF sensor to detect the distance from patient's forehead. This opening was then made into a window, using clear transparent polyvinyl chloride (PVC) plastic to create a barrier between the patient's skin and the ToF sensor. This window was added to improve the comfort of wearing the device and protect the ToF sensor from possible damage.

Results and Discussion

Software Components

The software of the CMS contains the code that controls the actions of the Arduino board and the ToF sensor, as shown in the system's functional flowchart in Figure 8 and Appendix B. After setup and initialization of the IMU, ToF sensor, and BLE capabilities, the Arduino board advertises as a peripheral BLE device. Once a connection is initiated by a central BLE device, the Arduino board begins reading accelerometry data from the board's IMU. If movement greater than 1.1 g-force units (g) in any direction is detected, then the start time is recorded. The threshold of 1.1 g was determined based on experimental use and ensures that the following loop is only entered when the device is picked up and placed on the head, not simply shuffled around. After the start time is recorded, the ToF sensor begins continuously reading range values. It continues to read range values until a range value of 50 millimeters or above is reached, indicating that the device has been removed from the head. The threshold of 50 mm was determined based on experimental use and ensures that the loop only breaks when the device is removed from the head and not when it is adjusted for fit or position. Once this threshold is reached, the device stops reading range values and records the stop time. The elapsed time is then calculated, by subtracting the start time from the end time, and then the elapsed time (in milliseconds) is written to the connected central BLE device. This process can repeat as many times as a large movement is detected while still connected to the central BLE device, ensuring that if multiple sessions occur in sequence, they will all be detected separately and accurately.

Figure 8. Functional flowchart for performance of the Cerebro Monitoring System (CMS).



In this application, there is one service containing one characteristic – elapsed time. Once a treatment session is activated and terminated, the Arduino board calculates elapsed time and advertises it as a characteristic. When a new treatment session is activated and terminated, the new calculated elapsed time becomes the new advertised characteristic and

replaces the old calculated elapsed time. This ensures efficiency and reduces power consumption on the part of the Arduino board, as it does not have to store more than one treatment session's data at a time.

Conclusion

This work sought to develop a first-stage prototype for remote adherence monitoring of a neurostimulation device using an IoT strategy. Components used include an Arduino Nano 33 IoT board, an Adafruit VL6180X time-of-flight sensor, a micro-USB battery holder, and a mobile device containing the LightBlue® BLE prototyping app and Adafruit IO Cloud Connect capability. These components, in coordination, are able to detect the initiation, termination, and elapsed time of a treatment session for a neurostimulation device. This data is then accessible via Adafruit IO Cloud Connect for remote researcher or physician viewing. Altogether, the CMS serves as a successful first-stage prototype for remote adherence monitoring of at-home neurostimulation therapy.

CHAPTER IV

CLINICAL TRIAL PROTOCOL DESIGN AND DATA MODELING

Introduction

The development of a clinical trial protocol and modeling of the data collected was informed by the insights gained through the stakeholder engagement process discussed in Chapter II. The technology developed in Chapter III forms the basis of the clinical trial design, as without remote adherence monitoring capability, it is difficult to elucidate accurate measurement of adherence. The protocol developed and discussed here is designed to test whether color and/or color choice of a device may influence adherence rates in pediatric ADHD patients to a statistically significant degree. Once the trial is completed and the data is collected, analysis modeling is conducted for three possible outcomes.

Materials and Methods

Development of Trial Protocol

A clinical trial was designed for the possible testing of two hypotheses- (1) choice of color of a device will statistically significantly increase adherence rates in ADHD patients aged 8-12 in an extraclinical environment, and (2) a specific color of a device will not statistically significantly increase adherence rates in ADHD patients aged 8-12 in an extraclinical environment. Participants should be recruited and pre-screened before scheduling a familiarization visit.

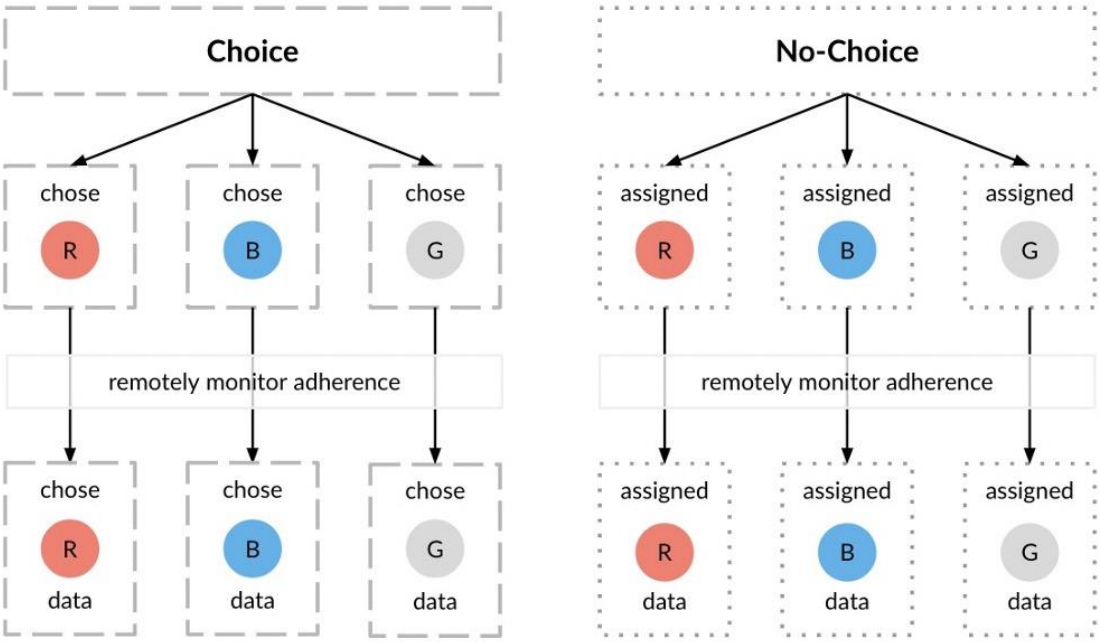
Pre-screening of participants for the trial includes limiting participants to children ages 8-12 who have a clinical ADHD diagnosis and full color perception abilities. Children and adolescents ages 8-12 were selected for study as the most popular segment for an ADHD-treating neurostimulation device, as identified in Chapter II. Children and adolescents with diagnosed ADHD will be required for this study because of the unique behavioral features that result from the symptoms of ADHD [2]. For example, children without ADHD may not have the same difficulty remembering or sustaining treatment tasks as would a participant with ADHD [2]. Thus, the largest improvement in adherence upon intervention is expected to be seen in children and adolescents with ADHD. Participants are also screened to only include those with access to mobile iOS devices, to ensure compatibility with the Cerebro Monitoring System (CMS).

After participants are screened and selected, they will be scheduled for a familiarization visit. During the familiarization visit, basic contact information and demographics are collected from the participant, as well as current medications, heart rate, blood pressure, height, weight, and BMI. Participants in the study will then need to complete the ADHD Rating Scale-V to verify their clinical ADHD diagnosis [107]. Additionally, participants should be screened for colorblindness using the Ishihara Color Blindness Test, to ensure they can distinguish between the colors of the devices [108]. Once it is verified that the participant meets all the inclusion criteria, assent is obtained from the pediatric participant and informed consent is obtained from the participant's parent/guardian on behalf of their child. Once the assent form and informed consent forms are signed, the participant and their parent/guardian will be instructed on how to operate

the device in detail, as well as given a take-home pamphlet for their future reference as needed. They will also be given the prescribed treatment time of 20 minutes per day for 10 consecutive days.

The participant will then be divided into either the “choice” cohort or the “no-choice” cohort based on a randomized drawing. “Choice” cohort participants will be offered three prototypes, one in each color, and will be asked to select the device of their choice, and then assigned their selected device for use in the at-home study. Devices for the “no-choice” cohort participants will be randomly assigned, and they will not be made aware that there are other color options. This structure is illustrated in Figure 9.

Figure 9. Proposed clinical trial cohort division.



After the familiarization visit is completed and the participant completes their 10 days of sessions with the device, the participant will return to the testing facility for a final visit to return the device. This clinical trial protocol is only proposed as one possible option for investigating the two above hypotheses, and thus from here on, fabricated data is used to simulate the possible outcomes of such a study as discussed in this section.

Data Analysis Methodology

The fabricated data, theoretically collected by the Cerebro Monitoring System in each device, was organized by participant and summed for a total elapsed treatment time value per participant. These values, the total elapsed treatment times, were compared to the total prescribed treatment time of 200 minutes (20 minutes per day for 10 days). The literature shows robust use of two primary formulas for measurement of adherence to pharmacotherapy – the medication possession ratio (MPR) and the proportion of days covered (PDC) [109-112]. MPR is most often calculated using Equation 1, while PDC is most often calculated using Equation 2.

Equation 1. Medication possession ratio (MPR) equation [110].

$$MPR = \frac{total\ days'supply\ of\ medication\ obtained\ during\ specified\ time\ period}{total\ number\ of\ days\ in\ specified\ time\ period} * 100$$

Equation 2. Proportion of days covered (PDC) equation [110].

$$PDC = \frac{total\ days\ during\ specified\ time\ period\ with\ adequate\ medication\ supply}{total\ number\ of\ days\ in\ specified\ time\ period} * 100$$

MPR and PDC are very similar but have one key difference – MPR can conceivably be greater than 100%, while PDC cannot. This is because of the key difference in the values' numerators. MPR can be skewed by early refills that increase the total days' supply of medication obtained during the specified time period while the total number of days in the specified time period stays the same. PDC maxes out at 100% because it cannot be skewed by early refills; an early refill does not alter the total number of days during the specified time period with adequate medication supply (i.e., days "covered" by medication supply). For this reason, PDC is often considered the gold standard for medication adherence calculation using pharmacy databases [110, 111]. Neither of these formulas is adequately adapted to the data collected by the CMS, and there is minimal literature about standardized adherence rate calculation for remote monitoring of device-based therapeutics. For this reason, a simple equation (Equation 3) was used for the calculation of an adherence rate of patients to the neurostimulation device.

Equation 3. Adherence rate equation.

$$AR = \frac{total\ elapsed\ treatment\ time\ (minutes)}{total\ prescribed\ treatment\ time\ (minutes)} * 100$$

Total elapsed treatment time was calculated by summing all the treatment sessions' elapsed treatment time values over the specified time period of 10 days. The total prescribed treatment time was 200 minutes, calculated by multiplying 20 minutes per day by the specified time period of 10 days.

Two-factor analysis of variance (ANOVA) with replication was run on the total data set and analyzed for statistically significant sources of variation, with a null hypothesis and alternative hypothesis as shown in Equation 4. Alpha for all following tests was set to 0.05.

Equation 4. ANOVA null hypothesis and alternative hypothesis.

$$H_0 : \mu_1 = \mu_2$$

$$H_a : \mu_1 \neq \mu_2$$

If the p-value obtained was less than alpha, the null hypothesis was rejected, and the source of variation was found to be statistically significant. If the p-value obtained was greater than alpha, the null hypothesis failed to be rejected, and the source of variation was found not to be statistically significant. If a source of variation was found to be statistically significant, then unpaired two-tailed pairwise student's t-tests were run to identify the statistically significant differences between groups, with a null hypothesis and alternative hypothesis as shown in Equation 5.

Equation 5. Student's t-test null hypothesis and alternative hypothesis.

$$H_0 : \mu_1 = \mu_2$$

$$H_a : \mu_1 \neq \mu_2$$

Power analysis was conducted for each t-test, to determine the number of participants needed to detect a given difference in the means. Equation 6 was used to determine the number of participants needed for a power of 80%.

Equation 6. Number of participants calculation using power and difference in the means.

$$n = \sigma^2 \frac{(Z_\alpha + Z_\beta)^2}{\Delta^2}$$

Input values included $\beta = 0.2$, difference in the means (Δ) = 0.1, and $\alpha = 0.05$.

Results and Discussion

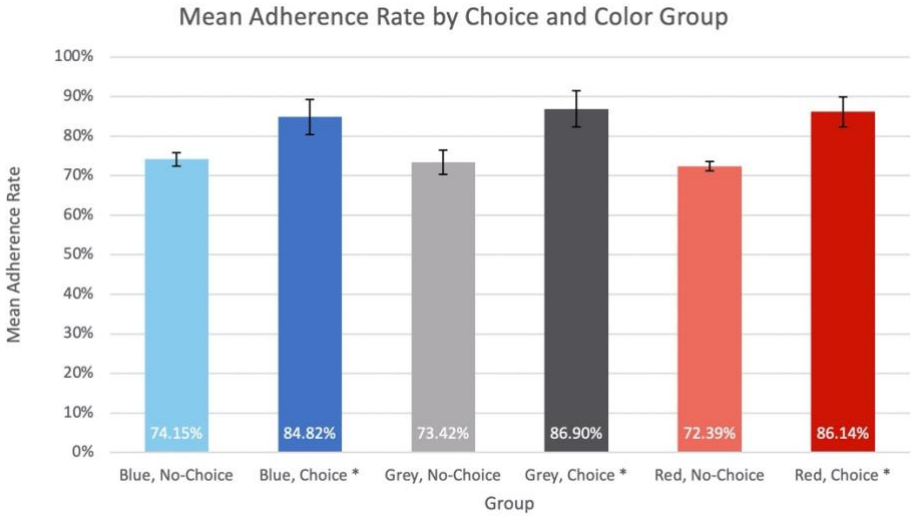
Selected Data Model 1

Model 1 represents one of the possible outcomes of the data- that color choice is a statistically significant variable in adherence rate, and that color is not a statistically significant variable in adherence rate. The data used for model 1 is shown in Table 2. Each group's mean adherence rate is graphed and labeled in Figure 10.

Table 2. Data used for model 1 analyses.

	Blue, No-Choice	Blue, Choice	Grey, No-Choice	Grey, Choice	Red, No-Choice	Red, Choice
Adherence rate	78.23%	85.84%	76.00%	81.89%	70.18%	80.50%
	75.71%	83.37%	70.98%	83.46%	75.30%	87.44%
	74.77%	91.05%	73.33%	95.01%	76.27%	88.39%
	71.09%	86.14%	69.13%	89.79%	73.41%	85.69%
	77.48%	75.11%	64.00%	93.00%	70.43%	90.40%
	69.95%	75.03%	73.33%	85.73%	72.51%	82.00%
	70.94%	85.17%	65.26%	97.20%	70.06%	94.00%
	70.10%	75.49%	78.78%	73.24%	73.38%	87.90%
	73.00%	94.23%	78.97%	93.40%	71.58%	83.49%
	76.52%	93.76%	73.33%	82.92%	69.48%	69.95%
	77.26%	76.82%	76.20%	73.65%	72.86%	89.06%
	74.75%	95.84%	81.67%	93.50%	73.15%	94.83%
Mean	*74.15%*	*84.82%*	*73.42%*	*86.90%*	*72.39%*	*86.14%*
Standard Deviation	*3.03%*	*7.83%*	*5.41%*	*8.09%*	*2.12%*	*6.69%*

Figure 10. Model 1 mean adherence rate by choice and color group.



Error bars represent the 95% confidence interval (CI) of each mean, calculated using Equation 7.

Equation 7. Mean confidence interval equation.

$$95\%\ CI = Z_{\alpha} * \frac{\sigma}{\sqrt{n}}$$

ANOVA was run on the data set and found the following p-values, as shown in Table 3.

Table 3. Model 1 ANOVA p-values.

Source of variation	p-value
Choice*	$4.999 \cdot 10^{-13}$
Color	0.865

Because the p-value for choice as a source of variation was less than $\alpha = 0.05$, the ANOVA null hypothesis (Equation 4) was rejected and this was found to be a statistically significant source of variation in the adherence rate data. Because the p-value for color as a source of variation was greater than $\alpha = 0.05$, the ANOVA null hypothesis (Equation 4) failed to be rejected, and this was found not to be a statistically significant source of variation in the adherence rate data. Statistically significant sources of variation are marked with an asterisk.

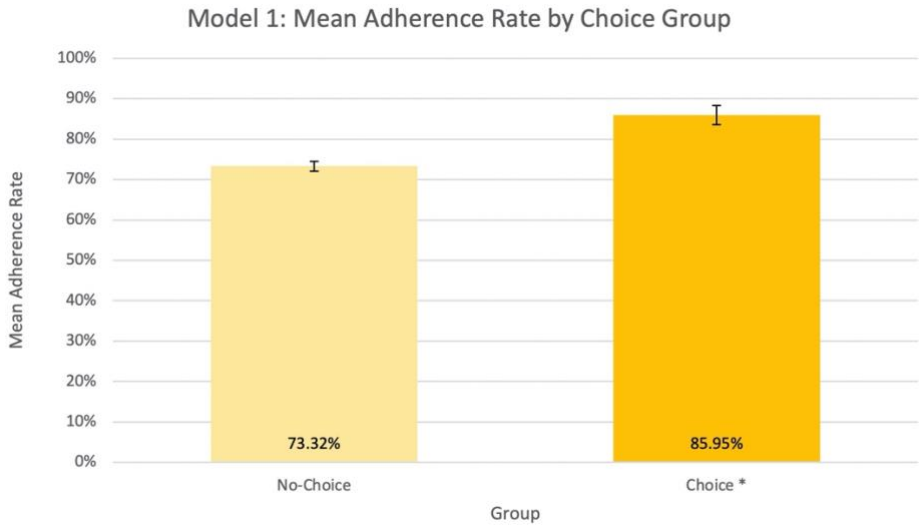
Because choice was found to be a statistically significant source of variation in adherence rates in model 1, an unpaired two-sided student's t-test was conducted between the choice and no-choice groups, as shown in Table 4.

Table 4. Model 1 t-test p-values.

T-test conducted	p-value
Choice vs. No-Choice	$2.11 \cdot 10^{-12}$

Because the p-value of this t-test was less than $\alpha = 0.05$, the t-test null hypothesis (Equation 5) was rejected and this was found to be a statistically significant difference. This finding is further illustrated in Figure 11.

Figure 11. Model 1 mean adherence rate by choice group.



Power analysis was conducted to elucidate the number of participants that would be needed per group to draw conclusions with at least 80% power (Equation 6). The data used in the above t-test between the choice and no-choice groups indicated that at least 5

(n = 4.53) participants per group (choice and no-choice) were needed for the test to be properly powered.

This model data indicates that choice is a statistically significant source of variation within the data, while color is not a statistically significant source of variation within the data. Further analysis via student's t-test indicates that the adherence rate of the choice and no-choice groups are statistically significantly different. These findings reveal that it could be helpful to offer aesthetic choices of medical devices to pediatric ADHD patients as a measure to increase adherence rates to treatment. It does not explicitly matter which specific colorways are offered to patients in the measurement of adherence rates, just that there are multiple aesthetic options offered.

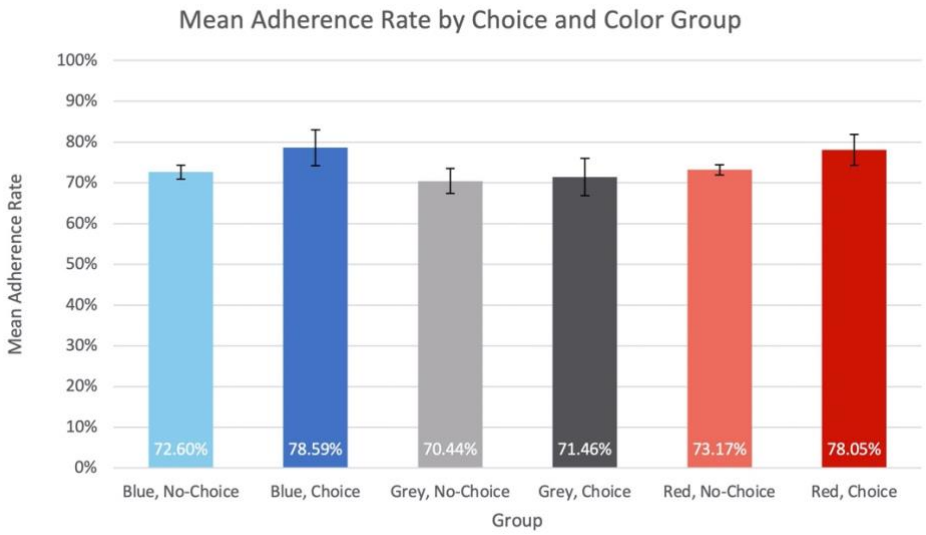
Selected Data Model 2

Model 2 represents one of the possible outcomes of the data- that neither color choice nor color is a statistically significant variable in adherence rate. The data used for model 2 is shown in Table 5Table 2. Each group's mean adherence rate is graphed and labeled in Figure 12.

Table 5. Data used for model 2 analyses.

	Blue, No-Choice	Blue, Choice	Grey, No-Choice	Grey, Choice	Red, No-Choice	Red, Choice
Adherence rate	77.44%	70.57%	63.83%	54.05%	60.58%	70.91%
	68.53%	99.87%	62.32%	62.10%	92.14%	87.44%
	68.19%	64.16%	60.56%	73.09%	67.32%	58.90%
	62.74%	78.88%	84.79%	98.59%	75.02%	85.69%
	80.00%	57.27%	57.77%	49.35%	83.52%	69.17%
	64.39%	80.84%	53.83%	88.05%	50.17%	82.00%
	79.87%	77.76%	59.88%	87.33%	75.13%	69.99%
	94.16%	63.09%	76.82%	61.34%	68.93%	75.21%
	69.08%	95.69%	64.33%	64.00%	93.78%	83.49%
	53.00%	86.12%	86.80%	64.80%	80.23%	69.95%
	98.35%	73.12%	76.86%	84.14%	61.73%	89.06%
	55.47%	95.70%	97.49%	70.66%	69.44%	94.83%
Mean	*72.60%*	*78.59%*	*70.44%*	*71.46%*	*73.17%*	*78.05%*
Standard Deviation	*13.98%*	*13.81%*	*13.75%*	*15.10%*	*12.91%*	*10.57%*

Figure 12. Model 2 mean adherence rate by choice and color group.



Error bars represent the 95% confidence interval (CI) of each mean, calculated using Equation 7. ANOVA was run on the data set and found the following p-values, as shown in Table 6.

Table 6. Model 2 ANOVA p-values.

Source of variation	p-value
Choice	0.215
Color	0.388

Because the p-values for choice and color as sources of variation were both greater than $\alpha = 0.05$, the ANOVA null hypothesis (Equation 4) failed to be rejected and these were both found not to be a statistically significant source of variation in the adherence rate data. Because of this, no additional t-tests were performed, and no power analysis was completed. These findings indicate that other device features and environmental factors should be considered and researched as possible influencers to increase patient adherence rates in a pediatric ADHD setting.

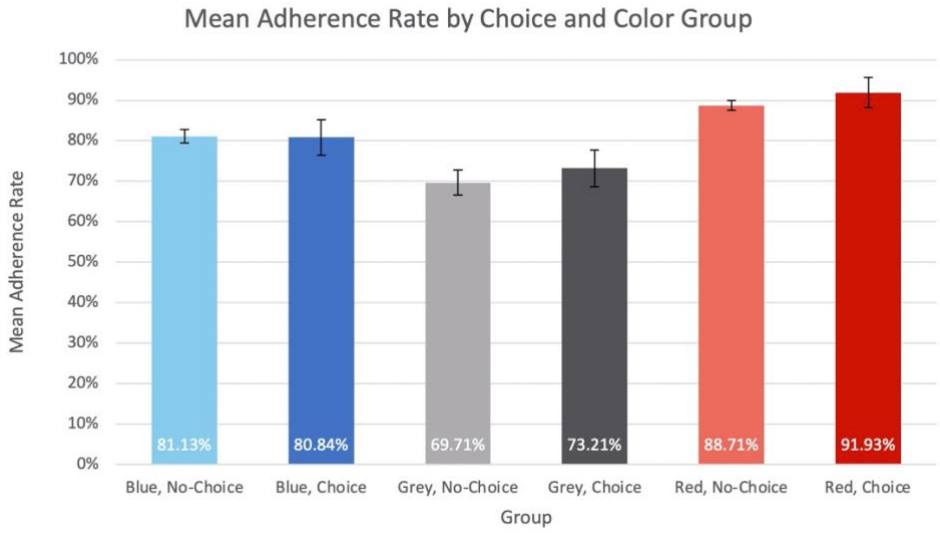
Selected Data Model 3

Model 3 represents the final of the chosen possible outcomes of the data- that color choice is not a statistically significant variable in adherence rate, and that color is a statistically significant variable in adherence rate. The data used for model 3 is shown in Table 7. Each group's mean adherence rate is graphed and labeled in Figure 13.

Table 7. Data used for model 3 analyses.

	Blue, No-Choice	Blue, Choice	Grey, No-Choice	Grey, Choice	Red, No-Choice	Red, Choice
Adherence rate	77.44%	70.57%	63.83%	72.10%	97.30%	96.54%
	68.53%	99.99%	62.32%	79.32%	94.67%	62.34%
	68.19%	64.16%	60.56%	71.20%	92.31%	99.60%
	98.96%	78.88%	68.97%	76.66%	75.02%	93.50%
	80.00%	89.08%	57.77%	76.20%	94.52%	97.30%
	64.39%	80.84%	69.64%	73.20%	80.32%	98.40%
	79.87%	77.76%	69.80%	87.33%	75.13%	89.99%
	94.16%	63.09%	76.82%	61.34%	93.20%	94.56%
	69.08%	95.69%	64.33%	64.00%	89.90%	93.01%
	86.90%	81.20%	86.80%	71.20%	80.23%	94.32%
	98.35%	73.12%	76.86%	75.32%	96.74%	93.24%
	87.68%	95.70%	78.76%	70.66%	95.20%	90.32%
Mean	*81.13%*	*80.84%*	*69.71%*	*73.21%*	*88.71%*	*91.93%*
Standard Deviation	*12.17%*	*12.24%*	*8.64%*	*6.77%*	*8.52%*	*9.77%*

Figure 13. Model 3 mean adherence rate by choice and color group.



Error bars represent the 95% confidence interval (CI) of each mean, calculated using Equation 7. ANOVA was run on the data set and found the following p-values, as shown in Table 8.

Table 8. Model 3 ANOVA p-values.

Source of variation	p-value
Choice	0.36
Color*	$5.25 \cdot 10^{-8}$

Because the p-value for choice as a source of variation was greater than $\alpha = 0.05$, the ANOVA null hypothesis (Equation 4) failed to be rejected and this was found not to be a statistically significant source of variation in the adherence rate data. Because the p-value for color as a source of variation was less than $\alpha = 0.05$, the ANOVA null hypothesis (Equation 4) was rejected, and this was found to be a statistically significant source of variation in the adherence rate data. Statistically significant sources of variation are marked with an asterisk.

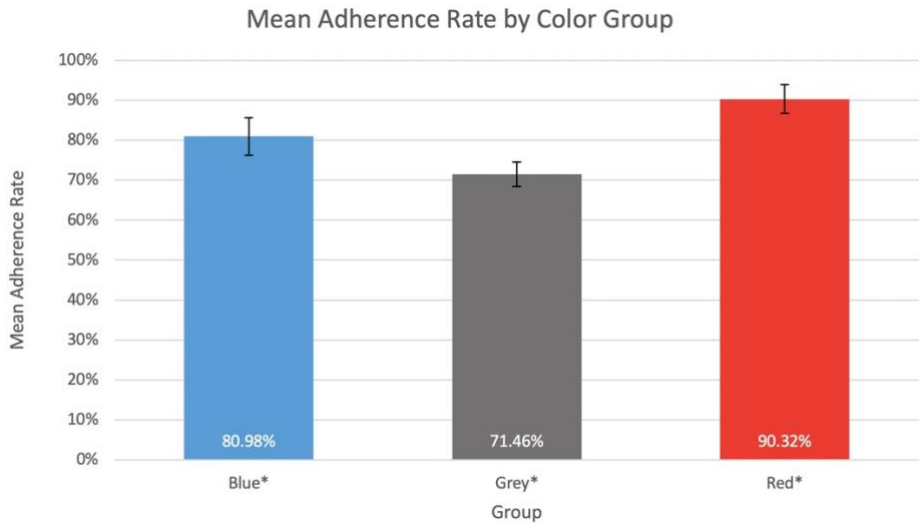
Because choice was found to be a statistically significant source of variation in adherence rates in model 1, an unpaired two-sided student's t-test was conducted between the choice and no-choice groups, as shown in Table 9.

Table 9. Model 3 t-test p-values.

T-test conducted	p-value	n
Blue vs. Grey *	$2.21 \cdot 10^{-3}$	7.42
Blue vs. Red *	$9.46 \cdot 10^{-10}$	9.76
Grey vs. Red *	$3.96 \cdot 10^{-3}$	8.03

Because the p-values of each of these t-tests were less than $\alpha = 0.05$, the t-test null hypothesis (Equation 5) was rejected for each pairwise combination and they were all found to be statistically significant differences. This finding is further illustrated in Figure 14.

Figure 14. Model 3 mean adherence rate by color group.



Power analysis was conducted to elucidate the number of participants that would be needed per group to draw conclusions with at least 80% power (Equation 6). The data used in the above t-tests indicated that at least 10 participants per group (blue, grey, and red) were needed for the test to be properly powered, as shown in Table 9.

This model data indicates that choice is not a statistically significant source of variation within the data, while color is a statistically significant source of variation within the data. Further analysis via student's t-test indicates that the adherence rates of the blue,

grey, and red groups are statistically significantly different. These findings reveal that it could be useful to offer red-centered colorways in a pediatric ADHD medical device in order to improve patient adherence to treatment.

Conclusion

The clinical trial protocol discussed above is designed to elucidate the effects of color and color choice of a neurostimulation device on adherence rates for pediatric ADHD patients. The data discussed is fabricated to model three possible scenarios as outcomes to the clinical trial and have different implications for future work. Model 1 (color choice is significant, color is not significant in influencing adherence rate) indicates that more work should be done to identify how color choice influences adherence rates, whether this hypothesis holds for additional populations and larger sample sizes, and if there is any relationship between the number of color choices and adherence rates. Model 2 (neither color choice nor color is significant in influencing adherence rate) demonstrates that more work should be done to identify other possible factors to influence adherence rates, such as awareness of monitoring technology, mobile reminders and notifications, or various form factors. Model 3 (color choice is not significant, color is significant in influencing adherence rate) signals that more work should be done to refine how color relates to adherence rate and which hues, tints, tones, and shades are most effective in influencing adherence rate. Overall, this clinical trial protocol is a powerful and relatively practical way to realize the possible effects of aesthetic design and aesthetic choice on adherence rates in a sample of pediatric ADHD patients.

CHAPTER V

CONCLUSIONS

Summary

ADHD is a neuropsychiatric disorder characterized by a combination of inattention, hyperactivity, and impulsiveness [2]. This body of work aims to explore the treatment environment of pediatric ADHD patients, innovate technology to mitigate identified pain points, and develop a clinical trial to further understand adherence rate patterns among pediatric ADHD patients. The first aim of this work was to conduct stakeholder engagement sessions through the Lean LaunchPad® methodology and customer discovery process. These sessions revealed a major pain point for pediatric ADHD patients in their current treatment options' side effects, high cost, and impermanence, which could possibly be mitigated with the development of neurostimulation therapeutic techniques. The second aim of this work was to develop a remote patient adherence monitoring system for implementation in a future neurostimulation device. This was accomplished using internet of things methodology, a time-of-flight sensor, and an Arduino Nano 33 IoT. The third and final aim of this work was to develop a clinical trial protocol to investigate the possible effects of color and color choice on adherence rates to a neurostimulation device in pediatric ADHD patients. Data models were created to represent potential outcomes in the data and their implications for the greater body of work.

Future Work

Additional work can be done in coordination with each of the chapters of this body of work.

In Chapter II, the stakeholder engagement results could be strengthened with the addition of more interviews, particularly those with parents and/or guardians of children with ADHD, as the children themselves are not particularly available for or willing to complete such interviews. Additionally, another round of customer discovery could be conducted with more precise questions to elucidate more exact pain points, desired solutions, and purchase options. Both of these supplementary propositions would require additional time, effort, and funding that was out of the scope of this body of work.

In Chapter III, future work should include the verification and validation of the Cerebro Monitoring System (CMS) as an accurate and robust tool for remotely measuring adherence rates. The code should also be made more efficient to reduce power consumption and enable the system to be used over longer periods of time. Future work should also include the development of a sturdy and adaptable housing for the CMS components to ensure its integrity through longer periods of use.

In Chapter IV, future work should include the carrying out of the clinical trial with a large sample size. This was out of the scope of this body of work due to time and funding constraints, as well as the ongoing COVID-19 pandemic, which greatly limited participant recruitment and engagement with a possible study. Possible future work based on the results of the clinical trial is discussed in detail in the conclusion of Chapter IV. This work

should include investigation into the relationship that pediatric ADHD patients have with medical devices and how this affects adherence rates overall.

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APPENDIX A

STAKEHOLDER INTERVIEW QUESTIONS

Problem: ADHD Treatment, Adherence Questions

1. Are you satisfied with the current ADHD treatments available to you?
2. What are the difficulties related to those current treatments from the patient's standpoint? From your standpoint?
3. With the current treatments, what do you feel the compliance rate is to your treatments?

Solution: Device Description Questions

The FDA has provided approval for neurostimulation devices for the treatment of various psychological disorders. We are especially interested in how neurostimulation devices for ADHD could be implemented in the clinic.

4. Do you think a device for stimulation for ADHD would be well-received among your patients? Your coworkers?
5. How do you think a device like that would impact or meet your criticisms of other treatment options?
6. If you were using a medical device as a psychiatric treatment for pediatric ADHD patients, would your clinic buy the device and lease/lend it out to patients? Or would patients purchase the devices individually from your office/or supplier?

Price & Go-to-Market: Payment Option Questions

7. Do psychiatric services fall in-network?

8. Given your experience, what would be a reasonable price for this therapy?
9. Do you think leasing devices from your clinic or having the patient purchase the device would affect compliance and adherence for treatment?
10. Do you think patients would be willing to purchase the device or pay for its treatment if the insurance does not cover the cost?
11. What are the current costs for drug therapy/prescriptions for patients currently using medication as a treatment for ADHD?

Concluding Questions

12. What do you wish I had asked?
13. Is there someone else I should talk to? Would you be willing to make an introduction?

APPENDIX B

ARDUINO NANO 33 IOT BOARD CODE

```
/*
  CEREBRO MONITORING SYSTEM

  Developed by William Delatte and Ally Camp for use by a Texas A&M University research team using Public
  Domain Documentation.

  This sketch is intended to establish a BLE connection and check for significant movement via the
  Arduino Nano 33 IoT accelerometry data. If a signficant movement is detected, the code begins reading data
  from the Adafruit ToF sensor and starts a timer. The ToF sensor continues to run until the experimentally-
  determined threshold is met, at which point the timer is stopped and the sensor stops reading data. The
  code then calculates the elapsed time and transmits this integer in ms to the BLE central device before
  returning to the BLE loop.

  The ToF sensor acts as a redundant use verification for whether the device is being worn.

*/


// Libraries to include in this sketch
#include <ArduinoBLE.h>       // include Nano BLE library
#include <ArduinoLowPower.h>  // include Nano LowPower library
#include <Arduino_LSM6DS3.h>  // include Nano accelerometer library
#include <Wire.h>             // includes library for I2C communication
#include <Adafruit_VL6180X.h> // include ToF sensor library

// BLE Setup and Initialization
BLEService elapTimeService("180F"); // BLE Elapsed Time Service Setup
BLEUnsignedIntCharacteristic elapTimeInt("2A19", BLERead | BLENotify); // Allow the central device to both read and be notified of data.

// declare and initialize variables
int previousRange = 0;
int previousElapTime = 0;
long previousMillis = 0;

// declare which pin to use for the LED
const int ledPin = LED_BUILTIN;

// SETUP LOOP
// only runs one time, right after the sketch is uploaded to the device
void setup() {


  // IMU initialization error print
  if (!IMU.begin()) { // if IMU fails to begin
    Serial.println("Failed to initialize IMU.");
    while (1);
  }

  // ToF initialization error print
  Adafruit_VL6180X vl = Adafruit_VL6180X(); // declare variable vl
  if (!vl.begin()) { // if ToF fails to begin
    Serial.println("Failed to initialize ToF sensor.");
    while (1);
  }

  // BLE initialization error print
  if (!BLE.begin()) { // if BLE fails to begin
    Serial.println("Failed to initialize BLE.");
    while (1);
  }

  // BLE local name, service, and characteristic setup
  BLE.setLocalName("elapTimeMonitor"); // write local name of peripheral device
  BLE.setAdvertisedService(elapTimeService); // add the elapsed time service UUID
  elapTimeService.addCharacteristic(elapTimeInt); // add the elapsed time integer characteristic
  BLE.addService(elapTimeService); // add the elapsed time service
  elapTimeInt.writeValue(previousElapTime); // set initial value for the elapsed time integer characteristic
  BLE.advertise(); // begin advertising the established services and characteristics

  Serial.println("Setup and Initialization Completed"); // will print once setup is completed
}
```

```
// MAIN LOOP
// runs constantly, for as long as the device is powered
void loop() {
  BLEDevice central = BLE.central(); // declare variable central

  if (central) { // if central is detected, print it out:
    Serial.print("Connected to central: "); Serial.println(central.address());

    while (central.connected()) { // while the peripheral is connected to the central, run awake loop:

      awake();

    } // end while (central.connected())

    // when the central disconnects, print it out:
    Serial.print(F("Disconnected from central: ")); Serial.println(central.address());

  } // end if(central)
}; // end void loop

// AWAKE LOOP
// runs when called in the main loop
void awake() {

  // Accelerometry variable declaration and initialization
  float x = 0;
  float y = 0;
  float z = 0;

  // Read acceleration values
  if (IMU.accelerationAvailable()) { // if the acceleration values are available, read them into x, y, and z:
    IMU.readAcceleration(x, y, z);
    delay(5); // pause for 5 ms between readings
  };

  // ToF variable declaration and initialization
  Adafruit_VL6180X vl = Adafruit_VL6180X(); // declare variable vl
  vl.begin(); // start vl
  uint8_t range = 0;
  uint8_t status = vl.readRangeStatus();
  int rangeVal = range;
  int Start_time = 0;

  // if significant movement is detected in either the positive or negative x, y, or z direction:
  if (abs(x) > 1.1 || abs(y) > 1.1 || abs(z) > 1.1) {
    Serial.println("Large shake detected, start reading range."); // print for testing purposes

    Start_time = millis(); // start timer - millis() returns the current # of ms since the program started running
    Serial.print("Start_time: "); Serial.println(Start_time); // print out the start time in ms

    // while the ToF range value is low (close to the head, less than 50 mm) and there is no no-converge error:
    while ((rangeVal <= 50) || (status != VL6180X_ERROR_NOCONVERGE)) {

      range = vl.readRange(); // read the ToF range into variable 'range'
      rangeVal = range; // set variable 'rangeVal' equal to variable 'range'
      status = vl.readRangeStatus(); // read the ToF range status

      Serial.print("Range: "); Serial.print(rangeVal); Serial.println(" mm."); // print out the current range value

      if (rangeVal > 50) break; // keeps reading range values until the range is above experimentally-determined threshold of 50 mm
    } // end while loop

    int End_time = millis(); // stop timer - millis() returns the current # of ms since the program started running
    Serial.print("End_time: "); Serial.println(End_time); // print out the end time in ms

    int Elapsed_time = End_time - Start_time; // elapsed time variable declared and calculated
    Serial.print("Elapsed time: "); Serial.print((Elapsed_time)); Serial.println(" ms."); // print out the elapsed time in ms.
    elapTimeInt.writeValue(Elapsed_time); // write Elapsed_time value to the BLE central device

  } // end large movement detection loop

} // end awake loop
```