Mentiva: A Methylphenidate-Based Treatment for Attention Deficit Hyperactivity Disorder with Low Incidence of Appetite Suppression

Final Design History File
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Prepared By:

Acui-Care, Team #4

Macy Fouch, Biomedical Engineer
Samuel Oh, Biomedical Engineer
Abby Puckett, Biomedical Engineer
Joshua Sodicoff, Biomedical Engineer
Danielle Wisner, Biomedical Engineer

BIOMEDE 450, Department of Biomedical Engineering, University of Michigan College of Engineering

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ACUI-CARE

Prepared For:

Dr. Melissa Wrobel, Chief Executive Officer of Pure Chemistry
Dr. Brendon Baker, Engineering Manager
Dr. Elizabeth Mays, Engineering Manager
Ms. Gurcharan Kaur, Engineering Manager
Mr. Samuel Jensen, Documentation Manager

Acui-Care would like to thank our engineering managers for their continued support throughout this semester. We would also like to thank our internal and external reviewers for their feedback on our design.

Note: Recurring "Design Updates" were kept in this Design History File to clarify changes to project goals and assumptions for readers on account of changes to aims over the course of the project.

I. EXECUTIVE SUMMARY

ADHD is the most commonly diagnosed neurodevelopmental disorder, affecting people of all ages. It can be treated by medication (most commonly a stimulant), therapy, or a combination of both. The Acui-Care team scoped to one of the most common side effects of stimulant medication, appetite suppression, which can reduce an individual's food intake while on their medication and lead to many health problems. This especially impacts patients taking extended-release formulations — a common type of medication taken daily that acts over 8-12 hours — as their appetite is suppressed for a large portion of the day. Our team has further scoped to adults rather than children because adults lack the comprehensive support system that children possess. Thus our team plans to design a solution to address the need to reduce the impact of appetite suppression in adult ADHD patients prescribed extended-release stimulant medications to ultimately improve patient wellbeing and tolerance of their otherwise effective medication regimen.

We have established three significant categories of user needs for our design, including safety, effectiveness, and accessibility, and have generated design requirements and specifications to meet those needs. Through extensive ideation, our team selected and outlined in detail three possible solutions that meet these design inputs, before ultimately electing to develop a combination of an existing stimulant product, Ritalin LA, and an off-label appetite stimulant, glipizide, for initiating an increase in appetite around lunch time.

In developing this solution, the team considered the properties of enteric coatings and pharmacokinetics of the medications utilized in order to formulate a manufacturing procedure to generate glipizide microbeads capable of quick release three hours after administration, which would be combined with existing Ritalin LA microspheres in a singular gel capsule. To further refine this design, a failure modes and effects analysis was conducted to determine its potential pitfalls and develop engineering solutions to mitigate these sources of failure. We additionally conducted a cost analysis to determine current patient costs associated with Ritalin LA, the manufacturing cost of our solution, and the patient cost of our solution in order to compare the overall estimated cost of our design to that of current treatment methods, namely original Ritalin LA.

To ascertain if our solution meets our design requirements, our team conducted both physical and paper testing. Our physical testing consisted of using the Hopfenberg equation to model the drug release of our microsphere core in Matlab for optimization of the microsphere radius and initial drug concentration values. Our paper testing plan consisted of developing a phase three clinical trial to validate the specifications of our critical, short-term requirements, particularly effectiveness for treatment of ADHD, reduction of appetite suppression, and overall tolerability.

The solution currently presented offers only the most simplified mechanism for addressing our team's critical, short-term goals; some potential future iterations for our design include replacing glipizide with another appetite stimulant to reduce associated risks and creating a version of our solution that can be safely marketed to the elderly population. In addition to these design modifications, Acui-Care recommends further in vitro and in vivo verification testing of drug release to remove current model simplifications and ensure accuracy of results. Furthermore, our current design does not meet our original long-term goals of increasing tolerability of and compliance to stimulant medication and expanding our market to include children and adolescents; these would be the principal goals for this project to address in the future.

Additional avenues for innovation of Acui-Care's current design could involve integrating solutions for other critical side effects of stimulant medications into our general design plan. Further recommendations from our team include utilizing a survey of stimulant users to gain more real-user perspectives, as well as basing all future work on a more thorough understanding of neuropharmacology and drug delivery than that possessed by the members of Acui-Care.

II. USER NEEDS

In this section, we will discuss ADHD and the population it affects, treatment options, causes of treatment noncompliance, as well as the biggest need facing patients with ADHD.

ADHD

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder commonly diagnosed in children, though it may persist through adulthood [1]. ADHD encompasses three types, inattentive, hyperactive/impulsive, and combined [2]. Inattentive type is characterized by poor listening, forgetfulness, distraction, and diminished attention span, whereas hyperactive/impulsive type is defined by fidgeting, restlessness, loudness, and difficulty waiting [2]. To be diagnosed with ADHD, a person must have at least five (or for a child up to the age of 16, six) symptoms (see Table 1) of either type for six months that present in multiple environments, as determined by a psychiatrist [2].

Affected Population and Comorbities. ADHD is the most commonly diagnosed developmental disorder, impacting 5.5 percent of children ages 3 to 17 in the United States in 1997 and having increased nearly every year to 9.8 percent of children in 2018 [1], or roughly 6 million children. ADHD can also affect adults, and in the United States, roughly 4.4% of adults have active ADHD symptoms [3]. While people with ADHD can live happy and healthy lives, there are multiple comorbidities associated with the disorder [4]. Two-thirds of adolescents with ADHD are diagnosed with a psychiatric disorder, most commonly learning and sleep disorders, oppositional defiant disorder, and anxiety, though treatment of ADHD with pharmaceutical interventions resolves these comorbidities in half of cases [6]. Adult ADHD is also frequently accompanied by psychiatric comorbidities, including major depressive disorder, anxiety disorder, substance abuse, bipolar disorder, and personality disorders [5]. Cotreatment of ADHD and comorbidities in adults has been shown to lead to better outcomes than treatment of comorbidities alone (without ADHD treatment) [5].

Table 1. ADHD encompasses two overlapping sets of symptoms, generally grouped into inattentive and hyperactive/impulsive types [2]. While symptoms vary, both reduce patient functionality in school and work environments.

Inattentive	Hyperactive and Impulsive
● Often fails to give close attention to details or makes careless mistakes ● Often has trouble holding attention on tasks or activities ● Often does not seem to listen when spoken to directly ● Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace ● Often has trouble organizing tasks and activities ● Often avoids, dislikes, or is reluctant to do tasks that require mental effort over a long period of time ● Often loses things necessary for tasks and activities ● Is often easily distracted ● Is often forgetful in daily activities	● Often fidgets with or taps hands or feet, or squirms in seat ● Often leaves seat in situations when remaining seated is expected ● Often runs about or climbs in situations where it is not appropriate (adolescents or adults may be limited to feeling restless) ● Often unable to play or take part in leisure activities quietly ● Is often "on the go" acting as if "driven by a motor" ● Often talks excessively ● Often blurts out an answer before a question has been completed ● Often has trouble waiting their turn ● Often interrupts or intrudes on others (e.g., butts into conversations or games)

Treatment of ADHD. ADHD is generally treated with neuropharmaceuticals [6]. Stimulants, a class of medication that inhibit the reuptake and thus increasing the concentration of norepinephrine, dopamine, and serotonin in the brain [6], are most commonly used and reduce symptoms noticeably in 80 percent of cases [6]. Norepinephrine reuptake inhibitors and adrenergic agonists are also prescribed [6] alternatively or in conjunction with stimulant medications, though they are known to work less effectively and for a subset of overall symptoms [7][8]. In addition to pharmacological treatments, ADHD can also be treated with behavioral therapy, generally cognitive behavioral therapy. Studies of cognitive behavioral therapy in adults have been found to result in significant changes in the Sheehan Disability Scale [9], a metric of functional impairment, with and without additional use of medication [10]. 15 percent of ADHD patients receive behavioral therapy alone, and 32 percent of patients will receive both pharmacological and behavioral therapy to manage their ADHD symptoms [11]. ADHD medications are generally prescribed for daily use [12], with stimulant medications being sold either in immediate release form, with an effective length of 3 to 6 hours, and extended release form, with a length of 8 to 12 hours. To avoid the inconvenience of redosing away from a caregiver (i.e. at school), children are often prescribed extended release formulations [12].

Treatment Noncompliance. Despite the range of treatments available for ADHD and their efficacy when prescribed with patient feedback, intervention noncompliance is common. In 2016, 5.7 million children ages 6-17 in the United States had been diagnosed with ADHD [11]. Of those 5.7 million, 62 percent were prescribed medication to treat their symptoms. However, despite medication effectively managing symptoms, it is estimated that up to 38 percent of patients prescribed ADHD medication will stop their course [14], with some studies estimating as high as 50 percent of all patients ceasing treatment without the remission of symptoms within 2-3 years of starting treatment [14].

Causes of Noncompliance. Studies of non-compliance have identified the adverse effects of medication as the primary culprit [14]. Associated concerns include stomach aches, insomnia, headaches, social

withdrawal and irritability. Additionally, perpetual stimulant medication can result in severe discomfort for patients who experience significant side effects. In addition to poor tolerance of side-effects, patients can demonstrate many other causes of medication noncompliance (see Figure 1). Some factors affecting compliance rates include the patient or caregiver, the process of being prescribed and medicated, the medication itself, and the patient's social and physical environment. Additionally, a patient may fail to comply with medication due to the limited medication options. Most ADHD prescriptions are extended release medications, lasting 8-12 hours in the body [12]. Depending on the severity of the side effects, the patient or caregiver may decide that the symptoms of ADHD are more tolerable than the medication side effects for that duration. Additionally, patients that experience ADHD symptoms inconsistently or only in certain settings (ie during exams, or specific times at school or work), may also avoid taking daily medication that affects them for 8-12 hours.

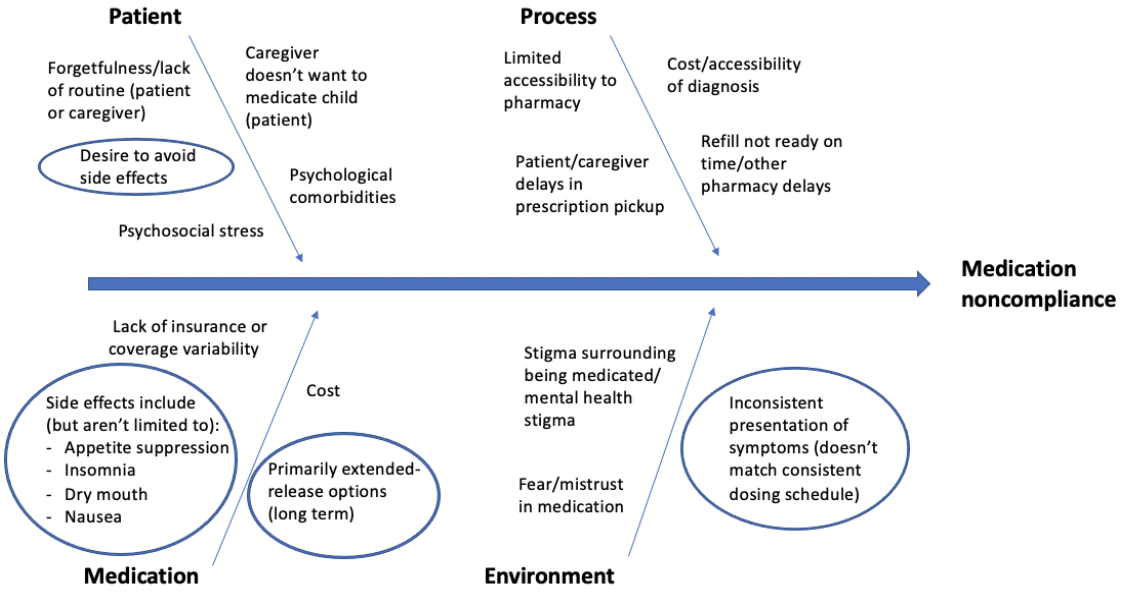

Figure 1. While the causes of medication noncompliance are multifaceted and stem from complex social and personal factors, adverse effects associated with treatment are most often reported as the reason for ceasing treatment. Circled factors indicate where we plan to innovate.

Task Analysis: Taking Medication. The process of being prescribed and taking medication can also affect medication compliance rates. To further understand the patient's experience and identify potential areas of improvement and intervention, we analyzed the steps a patient must take to be medicated for ADHD. After experiencing symptoms, the patient must visit their provider to seek treatment. If the provider believes the patient may be presenting symptoms of ADHD, they will recommend the patient to a specialist to get tested. After diagnosis, the provider will develop a treatment plan for the patient. If the patient is being prescribed medication, they will follow-up with the provider 30 days after the initial dose, and then at a frequency determined by the provider [15]. The patient can also make appointments to modify dosing or medication type with the provider as needed. After obtaining their prescription, the patient must establish a routine for dosing to experience optimal symptom relief. See Figure 2 for a detailed outline of the process of taking prescribed ADHD medication.

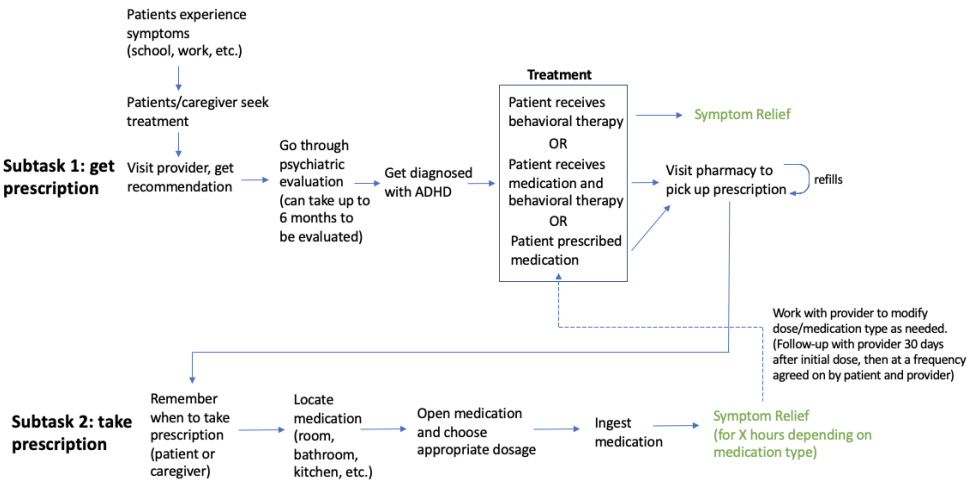

Figure 2. The process of getting treatment for ADHD includes diagnosis, development of a treatment plan (including prescriptions and/or therapy), consumption of medications and/or receiving therapy, and subsequent adjustment of treatment plan based on efficacy. The diagnosis and treatment adjustment phases are time intensive, whereas taking a prescription or attending therapy rely on developing a routine.

Need Statement

There is a need to reduce side-effect related noncompliance in ADHD patients prescribed extended release medications to ultimately improve patient compliance and functionality in daily life.

Market Analysis

In this section, we will analyze and discuss the market for pharmaceutical treatment of ADHD, relevant stakeholders, and current solutions.

Market Landscape

The global market for pharmacologic treatment of mental health disorders was estimated to be worth $49 billion in 2020 and was projected to grow at a compound annual growth rate of 4.8 percent every year until 2025 due to rising awareness and education surrounding mental health disorders. ADHD medications comprise a significant share of the mental health pharmacological therapies market; in 2020 the global market for ADHD medication was $18 billion and was projected to grow at a compound annual growth rate of 6.3 percent until 2025 [16].

Disease State. As awareness and recognition of ADHD continues to grow, the diagnosis rates are expected to continue rising as well. From 2003 to 2011 alone, ADHD diagnoses increased in children by 42% [17]. As with diagnosis rates, the use of stimulant medications is also increasing, and from 2006 to 2016 methylphenidate use increased 13%, and amphetamine use doubled [17]. Further, 60% of children diagnosed continue to experience symptoms as adults [18], thus many users of ADHD therapies are long-term users. As ADHD prevalence and diagnosis continues to increase, the market for ADHD therapies continues to expand as well.

Relevant Stakeholders. Most directly, ADHD affects the patients who are diagnosed with the neurodevelopmental disorder and who experience uncomfortable medication side-effects. If a patient is diagnosed during childhood, parents and caregivers may be involved in recognizing a child's symptoms, administering treatment, and managing medication side-effects. Primary care providers are responsible for evaluating a patient's symptoms and referring them to a psychiatric specialist for a screening and a possible diagnosis. After a diagnosis, psychologists, behavioral therapists, social workers, and other mental health professionals will be involved in the management and treatment of the disorder should the patient pursue therapy as a treatment option, and may be more heavily involved in the treatment process should the patient forgo medication due to side-effects and instead elect to use other therapies. Should the patient pursue pharmacologic therapy, pharmaceutical companies and pharmacies will be involved in the production and distribution of medications used for treating a patient's symptoms. Psychiatrists will be responsible for prescribing and adjusting medication dosage based on effectiveness as well as side-effect tolerability. Insurance companies will be involved in paying for treatment and may be impacted should a patient stop taking medication. Finally, teachers, peers, and colleagues may be affected or disrupted by a patients' symptoms at school or work and may have to adjust to changing treatment plans should a patient stop taking their medication.

Addressable Market. The total addressable market for a novel solution includes all patients who are diagnosed with ADHD and who are pursuing pharmaceutical treatment for their symptoms.

Target Market Segment. North America makes up the largest segment of the market at about 69% of the market share [16]; however, a novel solution could potentially benefit ADHD patients globally. When segmenting by age, we see that adults represent more than half of the total ADHD prescriptions, and noncompliance with ADHD treatment is also particularly high among adults [16]. Despite adults representing a large proportion of the non-complying population, ADHD is most commonly diagnosed and treatment plans are created during childhood, making a novel solution beneficial for patients of all ages. When segmenting by drug class, three categories emerge: stimulants, non-stimulants, and antidepressants. ADHD drugs are "highly genericized" and are typically "extended released" formulations [16]. Up to 30% of patients do not tolerate stimulant medications, and innovation in non-stimulant products is expected to drive future market growth [16].

Existing Solutions

A graphical dashboard of existing solutions (Table 2) highlights the current treatment options for ADHD patients. Included in the dashboard are various forms of ADHD medication, as well as various forms of non-pharmaceutical therapies.

Table 2: An overview of existing solutions for patients with ADHD who suffer from adverse effects, compared to both stimulant medications and Acui-Care's proposed solution. While nonstimulant medications generally have higher tolerability than stimulant medications, they generally only address a subset of symptoms and provide their own adverse effects. Nonpharmaceutical interventions have the ability to provide long-lasting relief to patients, but are limited by the high effort required to consistently engage in them and work for a smaller subset of patients.

			Nonstimulants			Therapies			Acui-Care
		Stimulants	Atomoxetine	Clonidine	Guanfacine	CBT	Coaching	Behavioral Interventions	Our Solution
Benefits	Increases focus	X	X			X	X	X	X
	Decreases fidgeting	X		X	X	X	X		X
	Alleviates emotional symptoms	X	X	X	X	X	X		X
	Exists in short acting formulation	X		X	X				NA
	Exists in long acting formulation	X		X	X				NA
	Works immediately	X		X	X			X	NA
Minimizes Adverse Effects	Non-drowsy	X	X			X	X	X	X
	No appetite reduction			X		X	X	X	X
	No sleep impact		X	X	X	X	X	X	X
	No increase in irritability			X	X	X	X	X	X

Medication. As discussed in the problem definition, ADHD is most commonly treated with stimulant neuropharmaceuticals. This class of medication has been proven to have short term efficacy in the majority of prescribed patients [19]. In adolescents prescribed stimulant medications, there has been evidence of increased short-term performance in school and at home [19]. In contrast to short-term benefits, long-term benefits of stimulant medication are not well-described. Studies have shown no academic or emotional status improvement after two years of taking stimulants [19]. Most active compounds are sold in both immediate and extended release formulations, with effects lasting 4 to 6 and 8 to 12 hours, respectively. Most notably, the biggest drawback of stimulant medications are the adverse side-effects, including but not limited to appetite suppression, insomnia, and irritability [19]. Appetite suppression is one of the most prominent issues as some studies have suggested that this has led to decreased growth in children prescribed stimulant medication [21]. Nonstimulants are also used to treat ADHD symptoms, but less commonly so, and are mostly prescribed in cases when stimulants do not adequately treat symptoms or the side-effects are not tolerable [14]. Atomoxetine is primarily prescribed for patients with inattentive subtype and takes several weeks of dosing before effects are noticeable [6]. Clonidine and guanfacine [6] are sedatives, prescribed for patients with hyperactive subtype. They are primarily prescribed for patients with high blood pressure.

Non-Pharmaceutical Therapy. Treatment of ADHD includes several forms of non-pharmaceutical therapy, including coaching, behavioral interventions, and cognitive behavioral therapy (CBT). Despite

these forms of therapy being widely used, their efficacy is controversial [19]. The most empirically supported form of behavioral treatment is CBT, which uses structured time with a therapist to identify links between thoughts, feelings, and behaviors [20]. Recent studies show that CBT can play a "very promising role" in improving patient outcomes. Although it does not show the same efficacy as medication, it has fewer side-effects and shows better cognitive results in adulthood [19]. Other forms of therapies are coaching, a direct approach to developing strategies to minimize the inconvenience of symptoms in specific environments, and behavioral interventions, which may allow ADHD patients to release excess energy by the means of fidget toys or sensory stimulation. These therapies do not introduce the side-effects introduced by medication, but may fail to effectively reduce symptoms and may not act immediately like stimulant medications.

Project Scope and Objectives

Long-term goals

Our long term goal is to address the adverse side effects of extended-release ADHD medication in order to improve treatment tolerability, functionality in daily life, and ultimately medication compliance. We aim to benefit the population of ADHD patients prescribed extended-release medications with a novel solution that ultimately reduces the percentage of patients that do not comply with their prescription after 2-3 years.

Short-term objectives

Our short term project objectives/user needs are that our solution must be safe, comfortable, and accessible. Each has several subgoals.

The top priority is the safety of our solution. To consider our solution safe, it must be reliable such that it consistently does what it is intended to do and has a low rate of malfunction. The design must also minimize the risk of misuse (e.g. having clear and uncomplicated instructions for use, etc). If applicable, the solution should have a long shelf-life and be inherently stable to reduce risk of being used after expiration. The safety of our solution is of top importance because we need to ensure that our solution does not expose users to any danger or risk of injury or death. If our solution is not safe for users, then it is not a viable solution to the problem.

The next priority is that our solution must be comfortable for users. A comfortable solution is one that does not interfere with the intended benefits of ADHD medication while also minimizing the adverse side effects from the medication. If our solution cannot do this then it is not a viable solution to the problem. Additionally, our solution should introduce very few or, preferably, no new side effects. There should also be minimal physical discomfort during administration of the solution. If our solution cannot meet these subgoals, then it will not be an attractive solution for users and many may choose other therapies.

The third priority is the accessibility of our solution. Our solution needs to be affordable for the majority of users. It must be easy to administer such that the process is clear, uncomplicated, and time efficient. It also needs to be usable independent of location. The solution should not increase the frequency of patients meeting their health care providers. If our solution cannot meet these subgoals, then it will be unavailable to a portion of the target market. A stretch goal in this category is that we would like our solution to be helpful for and usable by the entire population of ADHD patients, not just our target market.

In order to consider these user needs and their subgoals fulfilled, our solution must be comparable to or better than current treatment options in each category.

III. DESIGN INPUTS

Design Updates

After conducting more background research and interviewing another stakeholder currently prescribed a stimulant medication, we have further refined our scope. First, we plan to scope to the side effect of appetite suppression. Appetite suppression is commonly associated with stimulant medications [22], and in a 2-month study on methylphenidate, it was found that 70 percent of patients experienced appetite loss and 66.7 percent experienced weight loss [23]. Further, in the patients that experienced weight loss, there was a significant difference in the body weight and BMI of patients before and after treatment [23]. Additionally, our stakeholder (an adult living with ADHD) informed us that loss of appetite is one of the most noticeable side effects she suffers from, and her husband often has to physically "sit her down" and remind her to eat. As altered eating habits can affect many areas of an individual's health, including behavior, sleep patterns, nutrient levels and more, our team plans to address this problem.

Additionally, we plan to focus specifically on stimulant medications. A primary adverse effect of stimulant medications is appetite suppression[24], linked to increased dopamine levels in the nucleus accumbens [25]. Non-stimulants have their own associated side effects [26], some overlapping with stimulants including impact on appetite, though they are generally better tolerated and utilized by a smaller portion of the overall population. A solution focused on stimulants targets the most severe impact of appetite suppression with the broadest applicability.

Lastly, we plan to scope to the adult population (18+ years). Children often have little control of their dietary patterns, as their parent/caregiver or school is responsible for providing food for them and dedicating time for eating. Our stakeholder expressed concern for the population of adults who don't have someone that can remind them to eat when they aren't hungry. Even if the patient does have someone to remind them, those reminders may be inconsistent or infrequent, especially if the patient spends a significant portion of their day away from this person (i.e. at school or work). Without the physical reminder to eat (hunger), adults dealing with this side effect could go for extended periods without eating, thus causing additional health problems, including but not limited to anemia, infertility, bone loss, poor dental health, and decreased thyroid function [27]. Adults also make up the majority of the population medicated for ADHD [16], so our target market is still significant.

To reflect our recent changes, we have updated our need statement as follows:

There is a need to reduce the impact of appetite suppression on adult ADHD patients prescribed stimulant medications to ultimately improve patient wellbeing and tolerance of their otherwise effective medication regime.

Design Requirements

In this section we will discuss the requirements for our design. These features will be categorized into short-term and long-term as well as critical and non-critical.

Short-Term

Acui-Care's short-term design requirements are ranked from highest to lowest priority, with the first eight requirements being classified as critical and the rest as non-critical. Critical requirements were selected for their importance in either the usability of our solution for treatment of appetite suppression in parallel

to ADHD medication dosing or their applicability to a broad range of ADHD patients in the target market. A non-critical requirement was defined as one that is not necessary to solve the main problem but the inclusion of which would make our solution more attractive to users.

Critical

The critical design requirements are that the solution must be non-harmful, it must reduce the impact of appetite suppression, it must not reduce the effectiveness of ADHD treatment, there must be no increase in adverse effects, it must be personalizable, there must be limited interactions with medications prescribed for comorbid conditions, it must be physically stable, and it must not increase the frequency of healthcare visits. Each of these requirements will be explained in this section.

Non-harmful. Our top priority design requirement for our solution is that it must be non-harmful; it must not introduce any risk for the user during or after administration. We've identified this as a critical requirement because we need to ensure that our solution does not increase risk of injury or death to users. If our solution causes harm to users, then it is not a viable solution to the problem nor is it viably approvable by the FDA.

Reduces impact of appetite suppression. Our next requirement is that our solution must reduce the impact of appetite suppression from ADHD stimulant medication. As we discussed in our Design Updates section, our team has chosen to refine our scope to appetite suppression. Thus reducing the impact of this adverse effect on patients is the core goal of our project, making it a critical requirement for our solution. This requirement is intentionally nonspecific. By focusing on the impact of appetite suppression as opposed to suppression itself, the solution can take a broad range of forms that restore previous eating routines without the limitation of having to directly reduce the side effect itself.

Does not reduce effectiveness of ADHD treatment. Additionally, our solution must not reduce the effectiveness of ADHD treatment when our solution is utilized. This is critical because our solution is intended to be used in conjunction with existing stimulant medications that are effective for treating ADHD symptoms. Such an effect would either push patients to not utilize our solution or to drop medication regimes altogether, neither of which are positive outcomes as determined by the team. Thus, our solution should not interfere with the medication benefits to ensure the treatment plan does not become less effective for patients trying to manage their ADHD.

Does not increase adverse effects of ADHD medication. The fourth requirement is that our solution must not increase the number or severity of adverse effects experienced by patients. Our project was inspired by the high rate of medication noncompliance for stimulants due to their broad range of adverse effects. Our solution directly addresses a major side effect, but if it introduced more negative effects it would decrease the overall tolerability of the dosing regime, neither a satisfactory impact on patients nor one that would drive usage of the solution. The importance of the overall impact of adverse effects on our conceptualization of the need for our solution makes this a critical requirement for our solution.

Personalizable. Personalizability is also a critical requirement of our solution. ADHD patients span a wide range of sizes, health conditions, medication tolerances, and other factors that may be relevant depending on our ultimate solution. A solution that is limited in one of these categories would potentially exclude a large fraction of patients when some modifiability of a solution parameter (approved by a healthcare provider) would result in effective application.

Limits adverse interactions with comorbid psychiatric drugs. The sixth short-term requirement our team has identified is that our solution must have limited adverse interactions with medications commonly prescribed for comorbid conditions. ADHD patients often have comorbid conditions [4] and may be

taking medications to treat those conditions in addition to their stimulant ADHD medication. If our solution interferes with these common medications adversely, it would reduce tolerability of our solution for a large portion of our target market, one for which ADHD medications generally support reduced symptoms in their comorbid conditions [4]. Given our emphasis on the benefits of ADHD medication for this subset, it is critical they be able to continue all medication regimes while also utilizing our solution.

Physically stable. Another critical requirement of our solution is that it must be physically stable; it must not easily break or deform when subjected to reasonable force. There are two main reasons for this requirement: the user may be at risk of harm if our solution breaks during use, and there could be accessibility issues if frequent replacement is needed. These issues could arise from the expense of replacing our solution multiple times, the inconvenience of acquiring a replacement on short notice, the potential unavailability of a replacement at the time a break occurs, and so on. If our solution is physically stable, then users will be able to better integrate it into their daily lives, inside or out of their home, without being concerned that it will sustain damage. Our team is classifying this as a critical requirement because frequent breakage is a potential safety concern, and the accessibility issues that may arise would prevent a portion of our target market from being able to utilize our solution.

Does not increase frequency of healthcare visits. The final critical short term requirement our team has identified is that our solution must not increase the frequency of required healthcare visits for the users. Frequent healthcare visits may not be feasible for many people for a variety of reasons, including but not limited to inconvenient location of the healthcare office(s), schedule conflicts, and cost. Current treatment plans for ADHD already necessitate recurrent healthcare visits for clinical monitoring and evaluation of the treatment plan's tolerability [28]; further increasing this frequency could alienate a large portion of our target market due to inaccessibility. For this reason, our team has classified this as a critical requirement for our solution.

Non-Critical

Acui-Care has identified three non-critical, short-term design requirements, all relating to the accessibility of our solution. Our team aims to have a solution that is accessible to as much of our target market as possible, and thus it would be beneficial for our solution to be easy to administer, usable independent of location, and quick to administer. These three accessibility requirements are classified as non-critical by our team because their absence would not prevent our solution from safely addressing the main problem that we have scoped to, but their addition would make our solution much more attractive to and beneficial for users.

Easy to administer. Our solution should be easy to administer such that the process is not overly complicated and does not require much effort or mental ability; the hope is that users with a range of physical and mental abilities will be able to benefit from our solution, and that the potentially frequent use of our solution will not be a burden to patients.

Portable. It would additionally be advantageous for our solution to be usable in a variety of environments; a portable solution would allow more patients to have the freedom to customize their treatment experience to their daily lives and needs.

Quick to administer. Our team also intends for our solution to be able to be administered quickly. In order to prevent the solution from becoming an inconvenience for patients, the time it takes to administer our solution should be equivalent to the time (per day) it takes a patient to administer current ADHD medication.

Long-Term

Our team has identified two long-term design requirements that have both been identified as non-critical. These requirements will be discussed in this section.

Affordable. Our solution should be affordable for patients so that it is accessible to a large portion of the population of adults prescribed ADHD medication. We classified this requirement as long-term because we do not have the time to focus on making our product as cost-effective as possible. Additionally, we classified this requirement as non-critical. Our stakeholder stated that they would pay up to twice as much as what they currently pay for ADHD medication for a solution to appetite suppression. If stakeholders value the effectiveness of our product over the cost (i.e. they are willing to pay more for an effective solution), then we do not believe low cost is a critical design requirement.

Does not increase adverse effect related medication noncompliance. Our solution must not increase adverse effect related medication noncompliance. We aim for our solution to provide short-term relief from appetite suppression commonly associated with ADHD stimulant medications. Our goal is that relief from this adverse effect will increase medication compliance rates, however at a minimum, we hope to not increase noncompliance. As compliance is measured over extended periods of time and would require longer studies to measure, we classified this as a long-term requirement. Additionally, as there are many factors that cause noncompliance, we have classified this requirement as non-critical. We hope that our product will increase compliance by reducing a common side effect, but it is not a metric of our product's success.

Design Specifications

In this section we will discuss the specifications for our design. These features will be categorized into short-term and long-term as well as critical and non-critical.

Short-Term

First, we will discuss the short-term specifications associated with each design requirement.

Critical

The critical design requirements are that the solution must be non-harmful, it must reduce the impact of appetite suppression, it must not reduce the effectiveness of ADHD treatment, there must be no increase in adverse effects, it must be personalizable, there must be limited interactions with medications prescribed for comorbid conditions, it must be physically stable, and it must not increase the frequency of healthcare visits. Specifications for each of these requirements will be discussed in this section.

Non-harmful. First, our solution should not harm the patient. Adverse reactions to our solution should be "rare and uncommon." A review of adverse drug reactions defines "rare and uncommon" events as occurring in less than 1 percent of cases [29]. Additionally, half of adverse events typically go unreported [29], thus we aim to design a solution where less than (or equal to) .5 percent of patients report an adverse reaction. Our solution should also not cause life threatening adverse events. In a study between a control group (using no medication) and a group using our solution alone, there should not be a significant difference between the number of life-threatening adverse events. Essentially, our solution should not cause a number of life-threatening adverse events that is statistically significant.

Reduces impact of appetite suppression. Our design should decrease the impact of appetite suppression on patient diet. A Food Frequency Questionnaire [30] is a self-completed inventory of the frequency of a

wide variety of foods consumed over the course of a set time period, generally a week or a month. Such a questionnaire can be used to determine differentially consumed foods or food groups and can be used to gauge respondee nutrient consumption. Our solution does not aim to promote healthy eating, consumption of a specific range of calories, or anything else prescriptive of patient food consumption. Instead, Acui-Care intends to measure efficacy of the solution against the effects of appetite suppression by statistically comparing inventories completed by patients before and after beginning a stimulant ADHD medication regime and our solution. Success would be indicated by a lack of statistically significant difference between inventories as determined by a paired T test under these conditions over a month-long period, indicating no change in eating frequency as opposed to the decreased consumption resulting from stimulant medications.

Does not reduce effectiveness of ADHD treatment. Our solution should not decrease the effectiveness of coadministered ADHD treatment. The Conners' Scale [31] is a psychological tool relying on survey responses from potential ADHD patients and multiple stakeholders in their lives to measure the level of symptoms displayed. This metric accounts for multiple requirements of the ADHD diagnosis, namely the presence of symptoms in multiple environments and from both inattentive and impulsive/hyperactive subtypes. The resulting metric from the Scale is the T score, where a 60 or above indicates a likely ADHD diagnosis and 70 indicates serious difficulties in everyday life from the condition. As our solution is designed to only decrease appetite suppression from medications and not modulate their effect, we intend for there to be no significant increase in T score on account of administration. This would be determined by comparison of Conner's Scale responses for a patient with a paired T test before administration of our solution and after a month of regular usage.

Does not increase adverse effects of ADHD medication. Our solution should not increase the overall adverse effects experienced by a patient as compared to treatment with a stimulant medication alone. The FIBSER scale [32] is a self-reported measure of medication regime tolerability. Originally developed for analysis of pharmaceutical treatment of depression, the scale asks patients how much their medication interferes with everyday life. Generally, clinicians consider a score of 3 out of 6, indicating moderate interference with day-to-day activities, to be the threshold at which to modulate dosing regime. Our solution was broadly intended to decrease the adverse effects of stimulant ADHD medications. Thus, we consider no increase in FIBSER scale score a month after administration of our solution to indicate that adverse effects have not been increased by the solution.

Personalizable. Our solution must be able to be adjusted in dosage frequency to meet the needs of patients. Our stakeholder informed our team that deciding how and when to dose is very important for ADHD patients in order to not only maintain their focus as needed throughout the day, but also to limit the adverse effects experienced outside of school or work hours. As a result, treatment plans are highly individualized. Patients may choose to limit medication on days when little focus is required or may take additional medication throughout the day when extreme focus is required. Our solution must maintain this flexibility that current solutions offer patients so that it can complement their daily routines and schedules. In order to satisfy this requirement, our team has decided that our solution should allow the patient to use the product between zero and three times per day, depending on their needs. This matches current common medications such as Ritalin and Adderall which can be taken up to three times a day [33][34].

Limits adverse interactions with comorbid psychiatric drugs. Our design should also limit the adverse interactions with the drugs commonly prescribed for comorbid conditions. As adult ADHD is frequently accompanied by psychiatric comorbidities [5], we should expect that many patients will be undergoing co-treatment for ADHD and other psychiatric disorders. Since the goal of our project is to reduce side effects and increase patient tolerance of ADHD medication, our design should limit adverse reactions due

to interactions between our solution and other psychiatric drugs as well. Less than 0.5 percent of patients should report an adverse reaction with none being life threatening (see "Non-harmful" specification).

Physically stable. Lastly, our design should be physically stable and able to maintain its integrity while being subjected to daily wear and tear. Stakeholder analysis revealed that current ADHD medications are often thrown into a bag or backpack to be used outside the home. Therefore, our design should be able to withstand the physical impact of being "thrown around" in a backpack. It should not experience damage and should remain fully functional after being dropped to the ground. According to the American Academy of Pediatrics, a backpack should not weigh more than up to 20 percent of a person's body weight[35]; according to NASA's Anthropometrics and Biomechanics Man-Systems Integration Standards[36], the 95th percentile American man (age 40) weighs 98.5 kg. As 20 percent of 98.5 kg is 19.7 kilograms, this weight is expected to represent the typical upper weight limit of a backpack. The Ergonomics Center at NCSU[37] states that the 95th percentile male has an elbow height of 115.28 cm. As the typical motion of taking off a backpack/bag includes sliding it off the shoulder and releasing it from elbow height, our solution should be able to withstand being dropped from 115.28cm off the ground with a weight of up to 19.7 kilograms on it (assuming the solution is stowed at the bottom of the backpack) in all of our conducted trials. If our solution itself cannot withstand this impact, our solution should include a packaging or case to be used during travel that can meet this requirement.

Does not increase frequency of healthcare visits. Our solution should be accessible in terms of the frequency of healthcare visits needed for symptom monitoring and dose adjustments; use of our design must not increase the frequency of healthcare visits. As ADHD medication and dosing is highly individualized (see specification for "personalizable"), patients may be required to visit their healthcare providers very frequently when the medication is first being incorporated into their treatment plan. Regular clinical monitoring occurs monthly at the beginning of treatment and every three months once a stable dosing regime has been established. During these appointments, the provider will evaluate residual symptoms and tolerability, as well as side effects, heart rate, blood pressure, weight, and patient compliance [28]. Thus, our design must not require that ADHD patients utilizing our solution visit their healthcare providers more often than every thirty days, as a solution that increases the frequency of healthcare visits above the highest frequency seen in current solutions will not be attractive to our target market.

Non-Critical

Short term

In this section, we will discuss the specifications for each of the non-critical, short-term design requirements.

Easy to administer. The first non-critical design specification is that our solution must be easy to administer. Currently, medication in pill form is the most common method of treating ADHD symptoms; however, 15 percent of patients report difficulty with pill swallowing [38]. Ideally, our solution will not be more difficult than current solutions, and therefore the rate of patients reporting difficulty with administration will not be greater than 15 percent. This specification ensures that patients will not forgo our solution simply because it is more difficult or uncomfortable to administer than current solutions. Additionally, medication noncompliance as a result of difficulty with administration will not be introduced if administering our solution is as easy as administering stimulant medications.

Portable. Our design should be able to be used independent of location; in other words, it should be portable. In order for our design to be portable, it must be lightweight and small enough to be hand-held. According to the Department of Defense, hand-held, portable equipment is less than 2.3 kilograms in

weight with dimensions smaller than 100 mm x 255 mm x 125 mm [39]. Satisfying these specifications will ensure not only that our solution is transportable, but also that it is easy for the patient to transport without any inconvenience. Furthermore, ensuring that our design is portable will allow patients with ADHD to access it at any location, including home, work, or school, making it much more useful than a stationary design.

Quick to administer. Our final short-term requirement is that our solution should be quick to administer. To quantify this requirement, each member of our team simulated the amount of time it took for them to take a single dose of a pill. To do this, each member started a timer, acquired a pill bottle or compartment, consumed the pill with water, and returned the pill bottle to its original location before stopping the timer. As common stimulant medications can be taken up to three times each day, the average time of all team members was multiplied by three. It was determined that consuming current stimulant medications takes about six minutes each day. As a result, our team determined that the time it takes to administer our solution should not exceed six minutes per day.

Long-Term

In this section, we will discuss the specifications for each of the long-term design requirements. Note that each of these requirements is non-critical.

Affordable. Our first long-term goal is to make our solution affordable. Although ideally our novel solution's price would be comparable to that of current ADHD medications, after speaking with a stakeholder, it was established that many adults living with ADHD would be willing to pay more for a better solution that mitigated appetite suppression. Methylphenidate HCL and Amphetamine salt-based medications cost less than 2 dollars per dose [33][34], so our team determined that our solution should not cost more than four dollars per dose (or is not more than twice as expensive as ADHD medication over a period of time relevant to our solution).

Does not increase adverse effect related medication noncompliance. Our final long-term goal is that our solution does not increase medication noncompliance due to adverse effects. Currently, the compliance rate for ADHD medications over 5 years is 36 percent [40]. Although there are many reasons attributed to medication noncompliance, drug tolerability is cited as the most common reason for discontinuing treatment. Patients frequently experience adverse side effects such as appetite suppression, irritability, insomnia, and nausea; however, based on review of literature and the perspective of our stakeholder, appetite suppression stands out most prominently as the most severe adverse side effect experienced by adults living with ADHD. Although ideally ADHD medication noncompliance would be reduced with our solution, at a minimum our team hopes to not increase noncompliance above current rates. With our solution, at least 36 percent of patients should remain compliant with their ADHD treatment plans.

Prioritization and Presentation

Tables 1-3 below highlight Acui-Care's critical short-term, non-critical short-term and non-critical long-term goals, respectively, for our solution. The requirements and specifications listed are in the order of highest to lowest priority (within and between the tables), as decided by our team.

Table 1. Short-Term Critical Goals

User Needs	Design Requirement	Design Specification	Justification
Safe	Non-harmful	In a population of patients receiving our solution alone, less than 0.5 percent of patients experience an adverse reaction with none being life threatening.	A review of adverse drug reactions [29] defines events that occur in less than 1 percent of cases as "rare and uncommon." Half of that accounts for half of all adverse interactions going unreported [29].
Effective	Reduces impact of appetite suppression	There is not a statistically significant difference in responses to a Food Frequency Questionnaire recorded over a month in patients before taking stimulant medications and after taking stimulant medications and our solution.	Food Frequency Questionnaires [30] are a commonly used tool for measuring intake of foods by type and quantity over a set time period and allow for accurate quantitative assessment of diet consistency over time.
Effective	Does not reduce the effectiveness of ADHD treatment	Does not result in a significant increase in T-score (after 30 days of use) as measured by the Conners' Scale for ADHD assessment.	The Conners' Scale [31] utilizes responses from both patients and people with experience with patients across multiple environments to holistically determine severity of ADHD symptoms. An increase in T score, the derived metric, indicates an increase in ADHD behaviors.
Effective	Does not increase adverse effects experienced by patients	95 percent of patients see no increase in FIBSER scale	The FIBSER scale [32], although developed for patients receiving treatment for depression, is a generalized scale for medication regime tolerability, where a score of 0 corresponds with no issue with tolerability and 6 is inability to function on medication. An increase in score therefore means a decrease in tolerability, and a score above 2 is mild

			interference with daily life and is the upper bound for retaining a medication regime.
Accessible	Personalizable; the solution dosage frequency can be adjusted to meet the needs of patients.	The patient is given autonomy to use the product from 0 to 3 times per day, depending on their needs.	Common ADHD stimulant medications such as Ritalin[33] and Adderall[34] are taken up to 3 times a day. Stakeholder analysis revealed that the patient may choose to take additional medication throughout the day depending on their required level of focus for the day. This degree of flexibility should be matched so that the patient may use the proposed solution according to their personalized daily tasks.
Safe	Limits adverse interactions with medications commonly prescribed for comorbid conditions	In a population of patients receiving treatment for ADHD and at least one comorbid mental health condition, less than 0.5 percent more of patients experience adverse drug reactions over the course of a month than a population receiving treatment for ADHD	A review of adverse drug reactions [29] defines events that occur in less than 1 percent of cases as “rare and uncommon.” Half of that accounts for half of all adverse interactions going unreported.
Safe	Physically stable	Product should be able to withstand a 115.28 centimeter drop when placed at the bottom of a backpack that weighs 19.7 kilograms.	Stakeholder analysis revealed that medication is often brought with the patient in a bag/backpack, where it may be susceptible to physical impact. According to the American Academy of Pediatrics[36], a backpack should not weigh more than up to 20 percent of a person's body weight; according to NASA’s Anthropometrics and Biomechanics Man-Systems Integration Standards, the 95th percentile American man (age 40) weighs 98.5 kg[37]. As 20 percent of 98.5 kg is 19.7 kilograms, this weight is expected to represent the typical upper weight limit of a backpack. The Ergonomics Center at NCSU states that the 95th percentile male has an elbow height of 115.28 cm[38] when measured from the ground as to represent the typical taller end of the elbow height; as such, the typical

			distance a backpack is expected to drop is 115.28 centimeters when released from elbow height.
Accessible	Does not increase frequency of healthcare visits	The patient should not have to meet with their healthcare provider more than once every 30 days for purposes related to the proposed solution.	Monthly clinical monitoring is necessary at the beginning of treatment and after a stable treatment plan is established, monitoring must occur every three months. The proposed solution should not require a frequency of visits above the highest current frequency (every 30 days) to ensure it is at least as convenient and accessible as the existing treatment, and does not increase noncompliance.

Table 2. Short-Term Non-Critical Goals

User Needs	Design Requirement	Design Specification	Justification
Accessible	Easy to administer	Rate of patients reporting difficulty with administration is not greater than 15 percent.	Patients may not comply with using the proposed solution if the process to administer the solution is more challenging than the existing method of traditional pill ingestion. Roughly 15 percent of patients report difficulty with pill ingestion [38].
Accessible	Able to be used independent of location; portable	Less than 2.3 kilograms in weight. Dimensions should not exceed 100mm x 255mm x 125mm	Patients with ADHD are not guaranteed to be at home whenever stimulant medication is required, thus our solution should be portable. The weight and size of our solution should follow the MIL-HDBK-759C Department of Defense [39] standard for what is considered hand-held, portable equipment.
Accessible	Quick to administer	The time it takes to administer the solution does not exceed 6 minutes per day.	The stakeholder analysis revealed that additional doses of the stimulant medication may be taken throughout the day; common stimulant medications such as Ritalin and Adderall may be taken up to 3 times a day. Our team simulated single-dose administrations, and found it took an average of two minutes to ingest a pill. Our solution should therefore not take more than 6 minutes (2 minutes x 3 doses) per day to administer.

Table 3. Long-Term Non-Critical Goals

User Needs	Design Requirement	Design Specification	Justification
Accessible	Affordable	Does not cost over 4 dollars per dosage to use (or is not more than twice as expensive as ADHD medication over a period of time relevant to our solution).	Methylphenidate HCL and Amphetamine salt-based medications[31][32], the most common stimulant-based medications for ADHD, cost less than 2 dollars per dose. Our stakeholder said they would pay about twice as much as they currently do for their medication for an appetite suppression solution.
Effective	Does not increase adverse effect associated medication noncompliance	At least 36 percent of patients remain compliant with their ADHD treatment plans over 5 years of treatment.	5 year compliance with ADHD medication treatment plans is currently 36 percent [40], mainly attributed to issues with drug tolerability. At the very least, our solution must not increase noncompliance rates.

IV. DESIGN PROCESS

Design Ideation

In this section we will discuss the process of design ideation.

Brainstorming Narrative

Acui-Care's project began with an idea for an ADHD medication delivery system via a stimulant-infused fidget toy in early September. Since then, the project scope has changed significantly as the group has identified stimulant medication adverse effects as a more critical problem than novel delivery and selected appetite suppression in adults as a specific target for a solution.

Beginning to delve deeply into appetite suppression as a specific adverse effect, the team has become increasingly aware of the novelty of our solution. No products currently exist on the market with the expressed intent of reducing stimulant-caused appetite suppression in ADHD patients. In practice, concerns about tolerability generally result in changes to medication regime, often the inclusion or switch to a less effective nonstimulant medication, or complete noncompliance with the dosing regime. This has both proved a need for our solution, given the serious harm of reduced appetite over extended periods of time but also complicated the brainstorming process.

On September 30th, our team conducted a brainstorming session during which specific solution ideas were proposed. The brainstorming session was conducted casually, and our team adopted the mindset that "no idea is a bad idea"; as a result, all ideas were accepted and written down. Following the initial brainstorming session, our team began to look for trends in our list of ideas.

Orexigenic Stimulation. We first identified a pattern of addressing hunger directly. If focused directly on loss of appetite, a product currently used to stimulate appetite could sufficiently solve the problem. If continuous action of ADHD medication during mealtimes impedes consumption, a product that interrupts stimulant action temporarily could also improve appetite. Included in this category of ideas was building a gap between doses into an extended release medication, such that stimulant levels in blood would be reduced during meal time, however this path has been discontinued on account of the negative impact of the stimulant "come-down"[41]. This direction encompasses both pharmaceutical and nonpharmaceutical interventions to induce hunger.

Hunger Reminders. We also identified a pattern of reminding patients of their hunger. If awareness of physiological hunger in spite of the cognitive impact of medication could improve eating patterns, such a solution would effectively address our main aims while limiting the possible adverse effects of a solution that attempts to directly modulate hunger. We took inspiration from glucose monitors, used by diabetic patients to determine their dietary and insulin needs within the day. Measurement of biomarkers of physiological hunger or reduced nutrients in blood could be coupled with a notification system to tell patients when eating is necessary. A limitation of this avenue is that appetite suppression does not only encompass losing the desire to eat, but also results in decreased ability to eat due to nausea, so a solution would have to consider that encouraging eating will have to overcome adversity to consumption during stimulant action.

Miscellaneous Ideas. Finally, our group noticed several design concepts that fell under a broad range of categories. For example, in an effort to incorporate the needs and desires of our original stakeholder (see Stakeholder Interview Memorandum) we generated several ideas that incorporated aquatic therapy. Unfortunately, these ideas failed to meet the accessibility requirements discussed in our Design Inputs Memorandum. We also considered other devices or fidget toys that have been known to help mitigate

ADHD symptoms. Again, these ideas were eliminated on the basis that they did not meet one of our most important design requirements: that the impact of appetite suppression would be reduced with our solution. We finally identified brain stimulation to induce hunger as the only miscellaneous solution that addressed the impact of appetite suppression.

These directions will be elaborated on in our Design Concept sections.

Solution Limitations

Our team has recognized two limitations to be aware of in generating three concrete design concepts; these limitations will be discussed in this section.

Solution Complexity. Perhaps most critical in the process, the team has identified a strong upper limit on solution complexity. Current pharmaceutical interventions require dosing of stimulant medications between one and three times a day, or none in the event that a patient does not deem treatment of symptoms necessary on a given day, which is common and acceptable if productivity is not required. A solution much more complicated than taking a pill would significantly increase the time and effort required for treatment of ADHD and fail to meet the requirements of our solution being quick to administer and easy to administer, making utilization of our solution cumbersome and reducing the likelihood of solution acceptance.

Solution Impact. Furthermore, this illuminates that utilization of pharmaceutical interventions have a fairly limited impact on daily life, so a potential solution would have to be similarly noninvasive to promote acceptance. This also aligns with our requirements of being quick and easy to administer. While a feeding tube could certainly ensure a patient receives enough nutrition, no existing ADHD treatment requires anywhere near as much maintenance nor results in such a drastic change in daily life.

Design Concepts

With these considerations and our designated design specifications in mind, Acui-Care has developed three distinct design concepts — a pharmaceutical intervention for targeted appetite stimulation, an appetite monitoring device, and neurostimulation to induce appetite — to be elaborated on in the following sections.

Design Concept #1: A Pharmaceutical Intervention for Targeted Appetite Stimulation

Our first design concept is the addition of an appetite-stimulating medication to an extended release stimulant product. Ritalin LA, an extended release methylphenidate product utilizes Spheroidal Oral Drug Absorption System (SODAS), which allows for multiple medications in microbead form with enteric coatings to be loaded together into a gel cap for coadministration. The team therefore believed that a product with similar form but including a microbead formulation of an appetite stimulant would be an effective solution (see Design Justification). Acui-Care investigated a wide range of orally-taken medications with either the intended or unintended effect of appetite stimulation to be utilized in the solution. The details of formulating this design concept will be discussed in this section.

FDA Approved Appetite Stimulants.

The FDA has currently approved three drugs for use as appetite stimulants, generally for “wasting syndrome” from HIV/AIDS and chemotherapy. Dronabinol [42] is a cannabinoid, commonly sold as Marinol. While it consistently produces strong anti-nausea and appetite stimulating effects, it is mildly psychoactive in some users. Megestrol [43] is a synthetic form of progesterone, and oxandrolone [44] is a

synthetic form of testosterone. Both are more selective for their intended anabolic effects as compared to the progestogenic and androgenic effects, respectively, of their parent molecules, and have limited psychological effects but still have significant hormonal side effects, act continually instead of discretely, and require tapering if discontinued.

Off-Label Appetite Stimulants.

A wide range of medications have the potential to stimulate appetite and are used off-label for the purpose of appetite stimulation or for a different purpose with the effect of appetite stimulation. The set included below are representative of the major classes of medications with these effects and were selected for their benefits over other drugs in the class derived from our design requirements.

Mirtazapine. Mirtazapine [45], sold as Remeron, is an atypical tricyclic antidepressant commonly prescribed to individuals who have found other antidepressants intolerable for their common effects of appetite suppression and decreased quality of sleep. It commonly causes appetite stimulation via antagonism of the 5-HT_3 receptor and has been studied for that use in elderly patients [46]. Compared to other options, it has fewer physiological effects, but demonstrates more interactions with stimulants through risk of serotonin syndrome and requires more consistent dosing.

Cetirizine. Cetirizine [47], commonly sold as Zyrtec, is a selective H1 receptor inhibitor most frequently used for treatment of allergy-associated inflammation. It is not commonly used as an appetite stimulant, but antihistamines generally are known to increase appetite [48] and among them cetirizine is known to result in less drowsiness on account of its limited ability to cross the blood-brain barrier. It has limited physiological and psychological effects compared to other possible solutions and versatility in usage, but does not act very quickly nor is it particularly effective for appetite stimulation.

Glipizide. Glipizide [49], commonly sold as Glucotrol, is a sulfonylurea, capable of inducing insulin production in beta cells of the pancreas. It is not commonly used as an appetite stimulant, but its onset quickly induces a strong physiological hunger response. While glipizide may cause nausea on account of hypoglycemia if too high a dose is administered, it has the common side effect of weight gain in users due to increased hunger. Otherwise, glipizide compares favorably on appetite stimulation efficacy, psychological side effects, and its flexibility of usage.

Cannabigerol. Cannabigerol (CBG) [50] is a naturally occurring cannabinoid that is notable for its anti-inflammatory effects and limited psychoactive effects. Recent studies in animal models have demonstrated that it has a strong appetite stimulating effect [51] but it has not directly been studied for that purpose in humans, though it is safe and well tolerated in humans. While we know it has few side effects, takes effect quickly, and is mildly effective, too few studies have occurred to fully differentiate this compound from others.

Comparison of Appetite Stimulants. To compare the utility of these medications for determination of a candidate for use in pharmaceutical interventions, a sub-Pugh Matrix was utilized (Table 1). Dronabinol, as the most commonly used appetite stimulant, was chosen as the "gold standard" against which other options were compared. Limited physiological effects and stimulant interactions were highly weighted to ensure the solution would have few adverse effects on its own and be able to be used in combination with a stimulant medication. Next most important was appetite stimulation, for efficacy of the solution, and limited psychological effects, again related to our limited side effect requirement. Fast acting and short duration of action were next most important, as our design is intended to stimulate appetite for a short period corresponding to a meal. Finally, lack of withdrawals was weighed as the least important, as we assume patients will continue to use the product if it is effective.

Table 1. Sub-Pugh Matrix of Appetite Stimulating medications for use in Acui-Care Solution. Comparing against a commonly used appetite stimulant, dronabinol, we determine that megestrol, oxandrolone, and mirtazapine are worse than the gold standard, cetirizine is about the same, CBG is better and glipizide is the best, for the purpose of the project.

Attribute	Weight (1-5)	Dronabinol	Megestrol	Oxandrolone	Mirtazapine
Limited physiological side effects	5	0	-1	-2	1
Interactions with stimulants	5	0	0	0	-2
Stimulates appetite	4	0	1	1	-1
Limited psychological effects	4	0	2	1	0
Fast acting	3	0	-1	-1	-2
Acts for short duration	3	0	-2	-2	-2
Risks from regular use	3	0	-1	-1	-2
No withdrawals	1	0	-1	-1	-2
Score		0	-6	-15	-29

Attribute	Weight (1-5)	Dronabinol	Cetirizine	Glipizide	CBG
Limited physiological side effects	5	0	1	-1	1
Interactions with stimulants	5	0	0	0	0
Stimulates appetite	4	0	-2	2	1
Limited psychological effects	4	0	1	2	1
Fast acting	3	0	0	2	1
Acts for short duration	3	0	-1	1	0
Risks from regular use	3	0	1	1	0
No withdrawals	1	0	1	0	0
Score		0	2	23	16

Conclusions. Ultimately, glipizide was selected as the most feasible medication for utilization by a fair margin. It primarily prevailed on its efficacy as an appetite stimulant, its limited psychological effects, and its pharmacodynamic profile allowing quick, limited relief from appetite suppression. Although CBG was a fairly strong contender, studies in humans would be necessary to better validate and profile its appetite stimulating effects.

Finalized Design Concept

A solution utilizing glipizide would take the form of a time release medication co-administered in a capsule with a dosage of ADHD stimulant medication. The appetite stimulant would be released from microbeads after an enteric polymer coating dissolves due to a pH change. Variation in the length of delay

and dosage could be utilized to ensure patients receive an appropriate amount of drug at a time that matches a common meal time, for either lunch or dinner. Released just before the intended meal time, the drug would induce insulin production, causing a physiological and psychological response to low blood sugar strong enough to induce hunger. This design's principle of operation is absorption of the appetite stimulant from the lumen of the small intestine into the bloodstream. See Figure 1 for a layout drawing of this design concept.

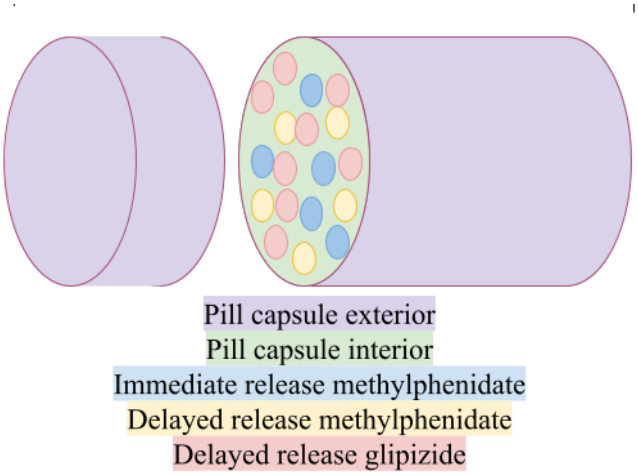

Figure 1. Concept Design Layout of pharmaceutical intervention. Modelled after Ritalin LA, an extended release methylphenidate product, the Acui-Care solution would include additional time-release glipizide in addition to immediate and time-release methylphenidate microbeads.

Design Concept #2: Appetite Monitoring Device

The second design concept that Acui-Care has investigated is the monitoring of hunger biomarkers to alert a patient when they need to eat. We based our research on blood glucose monitors and other monitoring techniques used to control diabetes, as a diabetic patient must know when they require a dose of insulin. Diabetes is a chronic condition in which either an insufficient amount of insulin is produced (type 1) or the insulin being produced is used ineffectively (type 2) [52]. Similarly, our design concept will operate by detecting one or more hunger monitors to alert the user when they need to eat. This design concept will be discussed in this section.

Hunger Biomarkers

Similarly to insulin monitoring, our team wants to utilize a monitoring system to detect when a meal is needed for the body. Based on monitors that rely on blood glucose to indicate when a patient needs insulin, we looked at a variety of biomarkers associated with appetite. Hormonal and biochemical biomarkers determined to have a strong relation with appetite include cholecystokinin (CCK), glucagon-like peptide 1 (GLP-1), glucose, leptin, ghrelin, and peptide YY (PYY) [53]. These biomarkers will be discussed and compared in this section.

Comparison of Biomarkers. To compare and contrast the different biomarker options, a sub-Pugh matrix (Table 2) was created using glucose monitoring as the baseline, due to the common use of glucose monitoring in existing diabetes treatments. The criteria considered is the relationship of the biomarkers to meal initiation or termination to detect appetite or detect overeating. This was deemed important by the stakeholder who specified that consuming food portions within a healthy range of size was desirable. Our

team also examined whether the measurement of the biomarker must be measured frequently, as biomarkers that rely on transient trends rather than absolute value measurements are more challenging to determine satiation and prone to misinterpretation by the device. Furthermore, frequent sampling may limit the potential for what sampling methods could be used to monitor the other biomarkers; some methods may take longer and may not be able to capture biomarker trends that are more dynamic and transient. The ease of detection of the biomarker is important as the device must be capable of determining the concentration of the biomarkers in the body in order to obtain the necessary data. Finally, the usefulness of the biomarker in short-term use is essential to determining whether the biomarker data would be relevant to the user within the upcoming mealtimes of the day.

Table 2. Sub-Pugh Matrix of Biomarkers in Appetite Monitoring for use in Acui-Care Solution. When compared against a commonly used biomarker for monitoring, we determine that while CCK is worse than the gold standard, ghrelin and GLP-1 are better than glucose for hunger monitoring purposes and can be used to gauge meal initiation and meal termination respectively. PYY and Leptin were eliminated from consideration prior to their inclusion in the matrix (see *Leptin* and *Peptide YY* for justification).

Biomarker	Weight (1-5)	Glucose	CCK	GLP-1	Ghrelin
Indicates hunger (Either meal initiation or meal termination to prevent overeating	5	0	0	1	1
Infrequent sampling	2	0	1	1	1
Ease of detection	3	0	-2	0	0
Short-term relevance for daily use	4	0	0	0	0
Score		**0**	**-4**	**7**	**7**

Glucose. Glucose monitoring is considered a feasible tool for hunger training to indicate when meals can be eaten [58]. Glucose levels in the blood are a good indicator of hunger, but rather than a given blood glucose concentration at a single point in time, dynamic decreases in blood glucose concentration over time (indicating decreased utilization and intracellular concentration of glucose) signal meal initiation [53]. Therefore, a solution utilizing blood glucose levels for the purpose of gauging hunger would have to be sampled frequently and detect such fluctuations.

Cholecystokinin. The presence of long-chain fatty acids and amino acids in the duodenum triggers the release of the gut hormone cholecystokinin (CCK) into the blood [54]. Studies involving CCK have determined that it is a general indicator of satiation, and is involved with the pathway that triggers meal termination. In the context of the project, a detected decrease in CCK levels may potentially indicate when sufficient time has passed since meal termination [53]. This correlation with hunger is what justifies an equivalent score of 0 with glucose as an indicator of hunger, and the lack of a need for dynamic CCK monitoring gives it a score of 1 in the infrequent sampling category. As CCK levels change after a meal, the levels of CCK are relevant to the short-term and therefore its score is on par with glucose. However, CCK is generally regarded as a challenge to monitor as it can appear in multiple molecular forms, some similar to that of ghrelin, and exists in relatively small concentrations [55]. Therefore, CCK is much worse compared to glucose regarding its ease of detection with a score of -2.

Glucagon-Like Peptide 1. Glucagon-like peptide 1 (GLP-1) is a hormone that is secreted in the presence of carbohydrates and fats [56], and stimulates the secretion of insulin to lower blood glucose levels after a meal [57]. GLP-1 reduces appetite, and is considered to be one factor that causes the sensation of fullness [53]. Its direct role in the hunger pathway as a form of meal termination means it is a better indicator of hunger relative to glucose and does not specifically require dynamic sampling, earning a score of 1 for both categories. As GLP-1 levels respond to each meal, measurements of GLP-1 are relevant to the short-term, also earning a score of 1 in that category. GLP-1 in the blood measurement is feasible and reproducible [53], suggesting that our project may use decreasing levels of GLP-1 as an indicator of when satiation is complete and suggest when the body is ready for another meal. It's ease of detection is on par with glucose, therefore giving it a score of 0 in that category.

Leptin. Leptin is a hormone released by fat tissue that reduces food intake [59]. However leptin concentrations were not found to have a correlation with appetite in subjects who were healthy (as quantified by having a stable body weight) [60]. Only in subjects with fluctuating body weights, leptin concentrations were found to have a negative correlation with perceived appetite [53]. As fluctuations in body weight are long term, leptin would likely be a biomarker that would have to be monitored long term rather than on a day-to-day basis. Therefore, leptin was immediately dismissed as a potential biomarker for this design concept, and was not considered in the sub-Pugh matrix (Table 2).

Ghrelin. Ghrelin is a hormone primarily produced in the stomach [61] and stimulates growth hormone release [62]. High ghrelin concentrations were found to be associated with greater appetites, and injections of ghrelin into human subjects had resulted in increased perceived appetite and food intake [63]. Monitoring ghrelin concentrations could potentially play a role in determining patient hunger. This gives ghrelin a score of 1 for being a direct indicator of hunger. Unlike glucose, it also does not require frequent sampling as absolute concentrations of ghrelin were used when in the clinical study demonstrating ghrelin's effect on hunger [63], earning a score of 1 for infrequent sampling as it would not need dynamic monitoring. In the same study, ghrelin levels were also shown to have an effect on individuals within the same day, earning a score of 0 for matching glucose regarding short-term relevance. Finally, its ease of detection in existing radioimmunoassays [67] [68] give ghrelin an equivalent score to glucose of 0 for that category.

Peptide YY. Peptide YY is a hormone secreted in the colon that ultimately inhibits the release of an appetite stimulant known as neuropeptide Y [53]. Injecting active PYY into lean and obese human subjects intravenously have led to a decrease in food intake by about 30% [64] within 2 hours of injection. While PYY is shown to suppress appetite, research on the viability of PYY as an indicator of appetite is lacking [53]. Therefore, PYY was immediately dismissed as a potential biomarker for this design concept, and was not considered in the sub-Pugh matrix (Table 2).

Conclusions. Overall, ghrelin and GLP-1 appear to be the superior biomarkers that would be measured as an indicator of appetite. Unlike glucose monitoring, neither biomarker requires the need to detect transient concentration changes to determine satiety. As higher ghrelin were correlated with greater appetite [63] and GLP-1 levels were indicated with meal termination [53], the monitoring of both of these biomarkers may be used to detect when the patient should either begin their meal and stop their meal to prevent overeating.

Finalized Design Concept

Therefore, a solution utilizing ghrelin and GLP-1 monitoring would likely resemble an existing glucose monitoring system, such as a wristwatch-esque device, in order to take samples from the patient at regular intervals throughout the day.

While there is no readily available continuous monitoring device for detecting GLP-1 and ghrelin concentrations, existing continuous glucose monitoring (CGM) techniques involve a subcutaneous needle with an enzyme-electrode system; the enzymes oxidize glucose molecules and the electrode detects the number of electron transfers, quantifying the concentration of glucose molecules [65]. Currently, radioimmunoassay techniques can be used to tag biomarkers with specific antibodies that can then be detected and quantified to determine relative concentrations; this technique is applicable to both GLP-1 [66] and ghrelin [67] [68].

Therefore, needles on the bottom face of the watch may take advantage of the antigen-antibody interactions and be used to detect relative amounts of GLP-1 and ghrelin via fluorescence or spectroscopy. Other potential avenues include the use of hydrogels that conform and alter their optical properties when in the presence of a particular biomarker, as is being experimented with glucose [69]. Ultimately, the watch display can be used to show time in addition to continuous biomarker data. Displaying time may be useful as it takes advantage of the resemblance to a wrist watch, can alert the user when it is close to a conventional meal time, and give the user a sense of when certain measurement values were taken. See Figure 2 for a layout drawing of our finalized design concept.

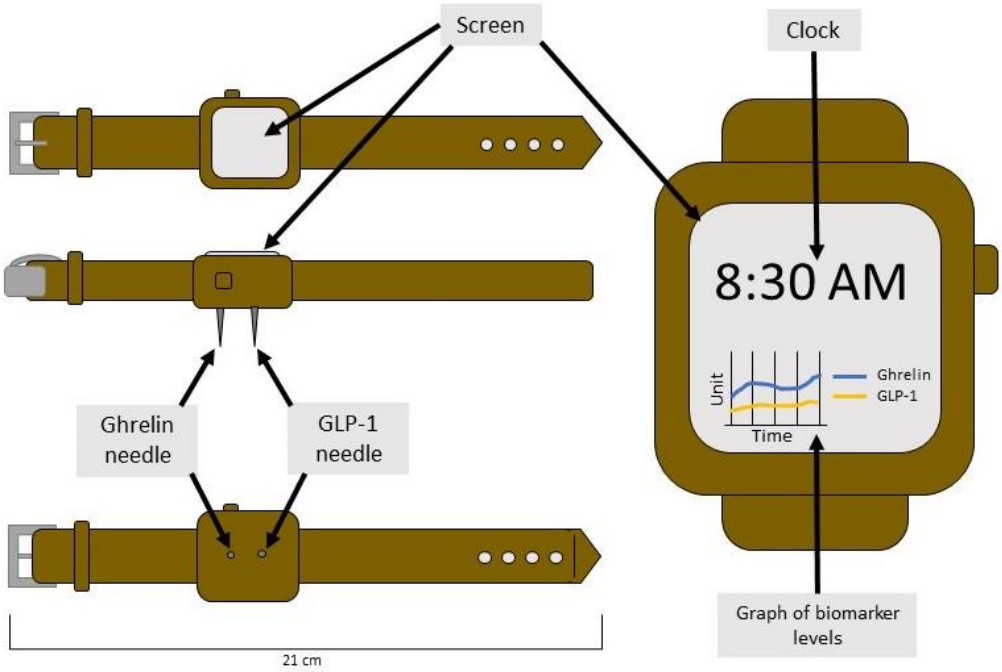

Figure 2. Concept Design Layout of Ghrelin/GLP-1 Monitoring Device, demonstrating the principle of operation of measuring hunger biomarkers. Two subcutaneous needles will utilize antigen-antibody interactions in order to detect the ghrelin and GLP-1 biomarkers. The display conveys time and monitoring information to the user.

Design Concept #3: Neurostimulation to Induce Appetite

The final design concept Acui-Care has developed is appetite induced by neural stimulation. Our team believed neurostimulation to be a valid concept as we found that neurostimulation via electromagnetic means have been used in studies to treat patients with eating disorders. Furthermore, a neurostimulation device for ADHD already exists. The one FDA-approved device that was relevant to both neural stimulation and ADHD treatment was the Monarch external Trigeminal Nerve Stimulation (eTNS) device by NeuroSigma, Inc [70].

Neurostimulation to Treat ADHD

In this section, we will discuss the use of neurostimulation to treat ADHD.

Monarch eTNS. The Monarch eTNS System comes in the form of single-use, disposable patches that are placed on the forehead [71]. This allows the device to generate electrical pulses that stimulate the Trigeminal nerve via noninvasive means, and is intended to be used when the patient is sleeping. While TNS has previously been seen used in treating epilepsy and major depressive disorder, children with ADHD aged 8-12 years old used TNS in a clinical trial in lieu of stimulant medications, showing substantial improvement as measured by the ADHD-IV Rating Scale [72].

Although the device was intended to address ADHD symptoms for patients who are not taking stimulant medication, the use of TNS in a double-blind clinical study has been shown to increase appetite, along with increased fatigue and headache as other side effects [73]. However, it is stated in the same study that the increases in reported appetite are not well understood and require additional testing [74].

However, the existing Monarch eTNS device was designed for use by children and not to specifically address appetite suppression [71]. Inspired by the existing use of nerve stimulation, our team investigated more focused methods of neurostimulation that target appetite specifically. Specifically, we found vagal nerve stimulation (VNS), nucleus accumbens (NAc) and subcallosal cingulate (SCC) deep brain stimulation (DBS), transcranial direct current stimulation (tDCS), repetitive transcranial magnetic stimulation (rTMS), and agouti-related peptide neuron stimulation (AGRP stimulation).

Neurostimulation to Treat Appetite Suppression

Comparison of Treatments. The different neurostimulation treatments were individually researched, as well as the studies that accompanied each technique's claims. We focused on whether the neurostimulation method would have a concrete effect on the user in terms of modulating appetite, the invasiveness of the procedure, and whether it has successfully worked on human adults. Other minor considerations included how frequent the neurostimulation would be needed.

Vagal Nerve Stimulation. One study examined the use of vagal nerve stimulation (VNS), in which the left cervical vagus is electrically stimulated via invasive means, to regulate appetite [74]. Near constant VNS via an implanted device was mostly shown to combat obesity long-term in minipigs (14 weeks) [75], however, and reduce appetite and prevent further weight gain rather than increasing appetite or reducing appetite suppression short-term [74]. However, the focus on preventing further weight gain (rather than promoting appetite) and the limited use so far on animals mean that this idea is not viable for our team to consider.

Deep Brain Stimulation. Another paper compiled studies that examined the use of deep brain stimulation (DBS) of two regions: the nucleus accumbens (NAc) and subcallosal cingulate (SCC) in the central nervous system. A single DBS procedure to stimulate both of these areas of the brain have shown to promote weight gain in individuals with anorexia nervosa [36], as demonstrated after a follow-up of 38 months [77] and 12 months [78] respectively. However, DBS is far too invasive for our team to consider.

Transcranial Direct Current Stimulation. Transcranial Direct Current Stimulation (tDCS) is a noninvasive technique that affects cortical and subcortical activity via electrical current across two electrodes that are placed on the skull [76]. One or more tDCS sessions lasting 20 minutes were shown to lead to a decrease in food craving [79] and desire to eat [80] nearly immediately after the session. Reduced eating had been observed to last up to 5 weeks after active tDCS [81]. So far, this option appears to be viable.

Repetitive Transcranial Magnetic Stimulation. Repetitive Transcranial Magnetic Stimulation (rTMS) is a noninvasive technique that can modulate activity in the dorsolateral prefrontal cortex (DLPFC), and repeated sessions of 10 Hz rTMS applied to the left DLPFC was shown to reduce cravings for food [42]. Continuous Theta Burst Stimulation (cTBS) is the continuous 50 Hz form of rTMS that was discovered to increase appetite for high calorie foods while not affecting appetite for low calorie foods in women after a week following a 2-hour stimulation session [83]. Therefore, rTMS can both increase and decrease appetite. The ability to both increase and reduce appetite has made rTMS an attractive option to the team.

Hypothalamic Agouti-Related Peptide Neurons. Hypothalamic agouti-related peptide neurons (AGRP) were discovered to induce the "voracious" desire to feed in mice when the neurons were photostimulated through an optical fiber implanted into the brain, taking only minutes [84] to act but stopping shortly after stimulation stops. However, the lack of experimentation (and the invasive nature of the procedure) has led our team to ultimately dismiss AGRP stimulation as a viable option.

Conclusions. Ultimately, the rTMS device was chosen for its ability to both increase and reduce appetite, giving this method an edge over the tDCS procedure. Furthermore, rTMS appears to be better than the existing eTNS device specifically when considering neurostimulation as a means to induce appetite, and potentially prevent overconsumption.

Finalized Design Concept

Existing rTMS technologies require the patient to visit a healthcare provider, as the machinery and technical skill currently needed to operate an rTMS does not appear to be feasible for a patient to learn, afford, or use [85]. Therefore, an Acui-Care solution that utilizes rTMS will likely have to be redesigned to be easy to use as well as able to be used at home.

Since existing literature supports the effects of rTMS on appetite when used on the dorsolateral prefrontal cortex, a potential device is a handheld probe capable of creating magnetic fields and can be held over the head. Furthermore, it would only need to be designed to create magnetic pulses at a continuous 50 Hz to promote appetite [83] as well as 10 Hz to decrease appetite if preventing overeating is a desired feature [82]. See Figure 3 for a layout drawing of our finalized design concept.

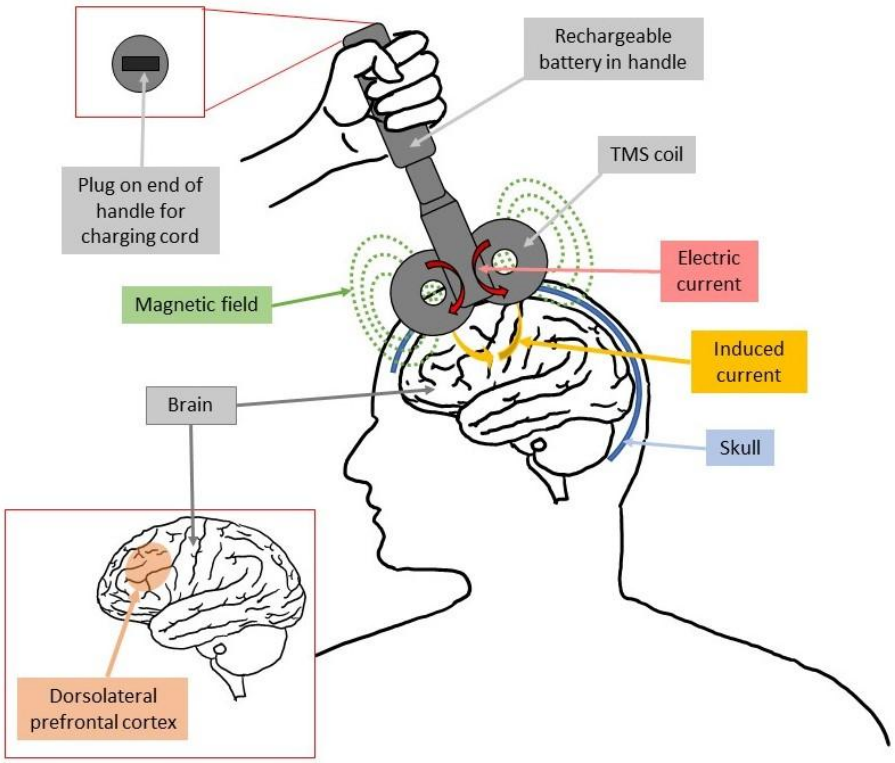

Figure 3. Concept Design Layout of rTMS Device, representing the principle of operation via induced neuronal current. While most rTMS devices are immobile and require visiting a doctor to utilize, a solution that could be effectively utilized for appetite stimulation and ADHD treatment by an adult would require portability and thus rechargeability.

Design Evaluation and Consensus

In this section we will discuss our evaluation process and criteria to select a primary design for our project.

Pugh Matrix Development

To compare our three design concepts, we utilized a Pugh matrix. Our gold standard and weighting of criteria will be discussed in this section.

Gold Standard. To evaluate our three concepts, we decided to use a baseline design of "no intervention" of appetite suppression. Currently, there are no widely used solutions for appetite suppression due to stimulant medications, and the current standard of care is to continue taking their stimulant medications without addressing the medication side effects (unless side effects are so intolerable that a medication change is required).

Weighting. In our concept evaluation Pugh matrix, we assigned five weights to our design inputs. As we had previously ordered our design inputs from most important to least important (as well as critical or non-critical, and short term or long term), we structured our weights to reflect this order of priority, with a weight of 5 reflecting the highest importance and a weight of 1 reflecting the lowest importance. We classified the "non-harmful" and "reduces impact of appetite suppression" design inputs as the most

important (weight = 5), because safety and effectiveness are our first priorities. Next, we classified "does not reduce effectiveness of ADHD medication" and "does not increase adverse effects experienced by patients" as a weight of 4, because although these are important aspects of our design and would affect the user's experience with our product, these inputs may be harder to control as they involve pharmacological interactions. Therefore, they are slightly less important than our "most important" group, but still of notable importance relative to our other inputs. Our next group (weight = 3), includes "personalizable" and "limits adverse interactions with comorbid medications," because these inputs are slightly less critical to our project's success than weight group 4, though still important to the user. In the next grouping of inputs (weight = 2), we included "physically stable" and "does not increase the number of healthcare visits." These two inputs are the last inputs on the short term, critical prioritization list. Lastly, we gave "easy to administer," "portable," and "quick to administer" a weight of 1, as these inputs constitute our short term, noncritical goals. We did not include our long term, noncritical goals in the pugh matrix, as our team deemed these inputs to be beyond the scope of our project under our current time limitations.

Design Concept Scores

In this section we will discuss the design concept scores assigned to each user need, as seen in Table 3.

Table 3. Pugh matrix comparing our three concepts to the baseline of no intervention for appetite suppression. Scores of -3 indicate "much worse" than the standard, while -2 indicates "worse" and -1 indicates "somewhat worse." A score of zero is equivalent to the standard. A score of 1 means "somewhat better" than the gold standard, 2 indicates "better" and 3 indicates "much better."

	Weight	Gold Standard	Pharmaceutical appetite stimulant	Hunger monitoring system	Neurostimulation to induce hunger
Non-harmful	5	0	0	0	0
Reduces impact of appetite suppression	5	0	3	1	2
Does not reduce effectiveness of ADHD medication	4	0	0	0	0
Does not increase adverse effects experienced by patients	4	0	-1	0	-3
Personalizable	3	0	0	2	1
Limits adverse interactions with medications commonly prescribed for comorbid conditions	3	0	0	0	0
Physically stable	2	0	0	-2	-1
Does not increase frequency of healthcare visits	2	0	0	-1	-2
Easy to administer	1	0	0	-2	-3

Portable	1	0	0	-1	-3
Quick to administer	1	0	0	-1	-3
Score		**0**	**11**	**1**	**-14**

Non-harmful. All of the design concepts proposed by our team will not be any more harmful than the gold standard of treatment, giving all three design concepts a score of 0. A solution that is harmful, in other words, if "rare and uncommon" events occur in more than 1 percent of cases, these designs are not a viable solution and will not be adopted.

Reduces impact of appetite suppression. A pharmaceutical appetite stimulant will be much better than the gold standard at reducing the impact of appetite suppression, giving it a score of 3. This is because an appetite stimulant will directly address appetite suppression by inducing a strong physiological hunger response in the patient. This will more effectively reduce the impact of appetite suppression than the hunger monitoring system, which will only serve to remind the patient to eat but not physiologically induce a hunger response, giving it a score of 1. Neurostimulation will induce a hunger response by modulating activity in the dorsolateral prefrontal cortex. This is a more direct approach than a monitoring system, but since neurostimulation can both increase and decrease hunger, it is less effective than a pharmaceutical intervention and receives a score of 2.

Does not reduce effectiveness of ADHD medication. Any non-pharmaceutical intervention will not interact adversely with ADHD medication, giving both the monitoring system and the neurostimulation a score of 0. Adding an appetite stimulant could potentially reduce the effectiveness of ADHD medications via drug interactions; however, it is known that glipizide does not interact with any ADHD stimulant medications [49].

Does not increase adverse effects experienced by patients. Compared to the gold standard of care, adding a pharmaceutical appetite stimulant may introduce adverse effects associated with that type of medication, giving it a score of -1. Some side effects of glipizide include low blood sugar, constipation, drowsiness, and dizziness, among others [49]. A hunger monitoring system serves purely as a reminder to eat, so it will not introduce any adverse effects experienced by patients, giving it a score of 0. Neurostimulation may cause transient headaches, local discomfort, dizziness, and rarely, seizures [86]. Because of the increased severity of neurostimulation side effects compared to a pharmaceutical appetite stimulant, neurostimulation receives a score of -2 in this category.

Personalizable. If the appetite stimulant is added to the ADHD stimulant pill, the pharmaceutical intervention will be just as personalizable as our gold standard, giving it a score of 0. If a hunger monitoring system is used, it will be more personalizable than the gold standard. This is because a monitoring system that measures biological indicators of hunger consistently will allow for more individualized detection and response than the gold standard, giving it a score of 2. Finally, if neurostimulation is used, it will be somewhat more flexible than our gold standard as treatment with neurostimulation can be adjusted based on the patient's needs.

Limits adverse interactions with medications commonly prescribed for comorbid conditions. The pharmaceutical appetite stimulant will not increase adverse effects due to interactions with comorbid medications. Glipizide (the appetite stimulant to be added to the ADHD medication) does not have any known adverse interactions with medications associated with comorbid conditions [49]. Since it will not increase the adverse interactions, it is equivalent to no intervention, which will not cause any negative interactions with comorbid drugs. The hunger monitoring system is also not introducing any chemical substances to the body as it is simply a monitoring device, and thus will not cause any drug interactions

(equivalent to no intervention.) Lastly, the neurostimulation device also does not introduce any chemical substances to the body, thus there will be no effects due to interactions between this solution and other possible drugs the patient is taking.

Physically stable. The pharmaceutical appetite stimulant will be integrated into the ADHD stimulant medication and thus will be as physically stable as current medication, giving it a score of 0 (no intervention for appetite suppression assumes the patient is still taking their ADHD medication). The hunger monitoring system will be less physically stable, because as a wearable device, it will be subjected to daily wear and tear that could potentially damage the device, giving it a score of -2. The neurostimulation device also could potentially be damaged (more so than a pill bottle), but since it is less portable than the other designs, it will likely experience less wear from use, giving it a score of -1.

Does not increase frequency of healthcare visits. The pharmaceutical appetite stimulant will not require increased healthcare visits after the initial appointments required to begin the treatment and thus will be equivalent to the number of healthcare visits for taking ADHD medication (no intervention for appetite suppression.) The hunger monitoring system has the potential to increase healthcare visits if the device is physically inserted into the patient's skin in some capacity for the purpose of monitoring biomarkers relating to hunger (similar to a glucose monitor for diabetes), giving it a score of -1. The neurostimulator device will definitely increase the amount of healthcare visits, as the current technology is administered by a technician. Even if we designed the device to be self-administered, it would likely require patient training and education, thus increasing healthcare visits overall and earning it a score of -2.

Easy to administer. Pharmaceutical appetite stimulation will be administered in conjunction with current ADHD medication, so it will not cause an increase in difficulty to administer and will be equivalent to no intervention, giving it a score of 0. The hunger monitoring system will require some upkeep, such as charging the device, and if it has to be applied by a medical professional, it will be harder to administer relative to no intervention, giving it a score of -2. The neurostimulator device will be much harder to administer relative to the simplicity of pill consumption, giving it a score of -3.

Portable. Pharmaceutical appetite stimulation will be administered in conjunction with current ADHD medication, so it will be equivalent in portability to current ADHD medication, giving it a score of 0. The hunger monitoring system will require slightly more care while moving it compared to just carrying a pill bottle around, however this device is still highly portable and will be designed to travel with the patient, resulting in a score of -1. The neurostimulator is not portable at all, and will remain at either the clinician's office or will remain at the patient's residence (if we improve the design to be self-administered), giving it a score of -3.

Quick to administer. The pharmaceutical appetite stimulation will be administered in conjunction with current ADHD medication, so it will be equivalent in administration time to current ADHD medication. The hunger monitoring system will require little daily maintenance, though it may require charging the device (if the device can be self-administered) or occasional visits to the healthcare office for device application, giving it a score of -1. The neurostimulator will be much less quick to administer than no intervention, as the device requires time to apply the electrodes and conduct the treatment (much more time than swallowing a pill), earning it a score of -3.

Consensus

After our Pugh matrix scoring, we have found that the pharmaceutical appetite stimulant is ranked the highest with a total score of 11. The hunger monitoring system comes in second with a total score of 1, and the neurostimulator tool comes in last with a total score of -14. Therefore, our team will proceed with the pharmaceutical appetite stimulant design.

V. DESIGN OUTPUTS

Detailed Design

Our final proposed design is a delayed-release appetite stimulant embedded within an ADHD stimulant. The details of our design will be discussed in this section.

ADHD Stimulant Delivery

We will be using methylphenidate (MPH) as our ADHD stimulant. Specifically, we will be using a form of extended-release methylphenidate called Ritalin LA, which is comprised of methyl α-phenyl-2-piperidineacetate hydrochloride (also known as methylphenidate hydrochloride) [87]. Though Ritalin LA is an extended-release formula, it has the effect of two immediate release doses, resulting in two peak blood plasma concentrations throughout the day, one at roughly 1 hour post dose and one at roughly 6 hours post dose [88]. Target efficacious blood plasma concentrations will vary based on dose; however, typical blood plasma concentrations range from 2 ng/mL to 14 ng/mL for patients receiving between 10 and 60 mg of MPH, as seen in Figure 4. Toxic concentrations are not well reported; there is only one known death attributed exclusively to MPH overdose. This patient's blood plasma concentration was around 1000 ng/mL of MPH [89]. However, it is not recommended for patients to take greater than 60 mg of MPH and therefore we aim for MPH concentration to not exceed 20 ng/mL, as this accounts for some variability from the blood plasma concentration curves seen in Figure 4 but is still well below potentially toxic concentrations.

Our initial design will contain a total Ritalin LA dose of 20 mg, which is the typical starting dose of MPH for ADHD patients [90]. However, this design could also be applied to varying doses of both the appetite stimulant and Ritalin LA (which currently is offered in amounts of 10, 20, 30, 40, 50, and 60 mg). The release profiles of these different doses and their bimodality can be seen in Figure 4.

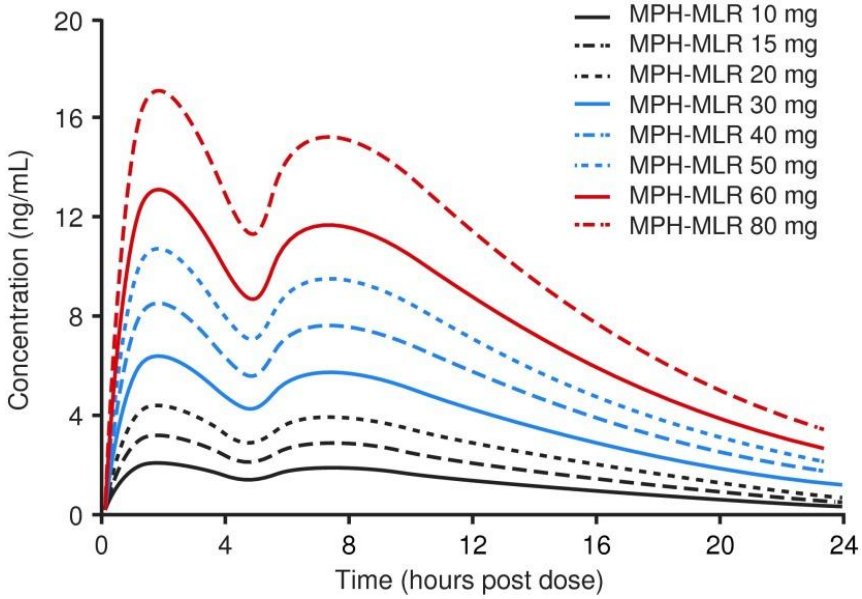

Figure 4. Time-concentration curve for Ritalin LA-like product at multiple doses. At all doses, there are relative maximum concentrations at 1 hour and 6 hours. While concentration decreases between released doses, it does not drop low enough to reduce appetite suppression. Taken from [88].

Ritalin LA uses Spheroidal Oral Drug Absorption System (SODAS) technology to deliver the drug. Each capsule is filled with beads, half of which are immediate-release beads with the other half are enteric-coated beads designed for delayed release. The immediate release beads consist of a methylphenidate core with no coating, allowing the drug to begin release once it enters the gastrointestinal tract. The delayed release beads are coated with ammonio methacrylate copolymer and methacrylic acid copolymer [91] to prevent release of the drug until it reaches a specific part of the intestine [92].

Appetite Stimulant Delivery

In addition to including both the immediate and extended release beads (of 10 mg MPH each), our design will also include 5 mg of glipizide in microbead form, coated with Eudragit S-100 polymer to ensure delayed release of the drug. (Note: we will not be modifying the Ritalin LA beads in any capacity). The glipizide microbeads will consist of glipizide and sodium alginate (a coagulant) in a 1:6 ratio (see Figure 5 for layers of each microbead in our drug) and will be < 800 μm in diameter. In the next two weeks, we plan to model the release profile of the glipizide microbeads and choose a radius that most closely matches the release profile of traditional glipizide drug release. Current studies of glipizide microbeads produce radii in a range from 1-400 μm. The thickness of the Eudragit S coating will be roughly 40 μm, as this is the thinnest coating possible while using current fabrication processes. A thin coating is ideal as it will achieve the fastest drug release possible once the drug reaches its target location.

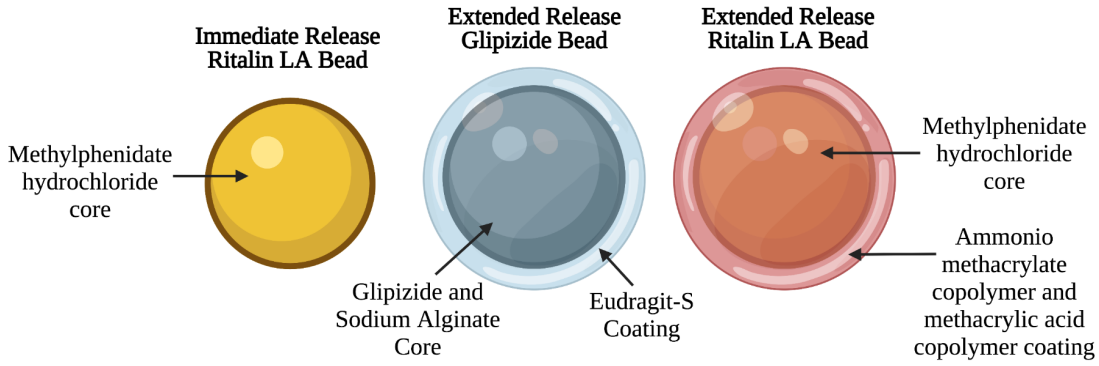

Figure 5. The immediate release methylphenidate hydrochloride beads (Ritalin LA formulation) will be uncoated, the extended release methylphenidate hydrochloride beads will be coated in an enteric ammonia methacrylate and methacrylic acid copolymer (Ritalin LA formulation), and the extended release glipizide beads will be coated with Eudragit S.

Targeted Release Profile for Glipizide Beads. Our glipizide microbead release profile should closely resemble the release profile of a 5 mg glipizide tablet (as tablets are the current form of glipizide administration and 5 mg is our starting dose). Currently, immediate release formulations of glipizide demonstrate a peak in blood concentration, while the extended release formulations maintain roughly constant plasma concentrations (see Figure 6). We want to achieve appetite stimulation during the middle of the day only (not constantly throughout the day), therefore we want the plasma concentration of glipizide to peak during lunch hours.

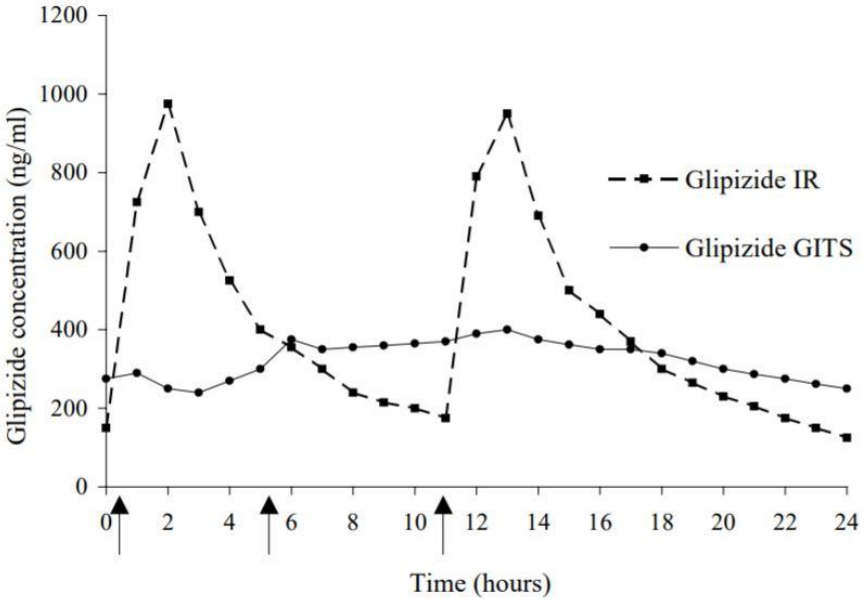

Figure 6. Time-concentration curve for glipizide products. Glipizide IR corresponds to immediate release glipizide administered twice, at the 0 and 11 hour marks corresponding to peaks 2 hours later, whereas Glipizide GITS is an extended release formulation resulting in approximately constant concentration over a day. Taken from [93].

Glipizide follows a Fickian diffusion mechanism and is best described by the Higuchi Model [94]. The Higuchi model relates fraction of drug released to the square root of time multiplied by the experimental Higuchi release constant (see Appendix A for equation and constant values). We used Matlab to plot the release of 5 mg of uncoated glipizide in tablet form (see Appendix A for Matlab code). The results demonstrate that nearly all of the drug is released in less than one hour (see Figure 7), which is consistent with in vitro studies of the drug [94]. This is the release profile we will try to resemble when optimizing the microbead radius.

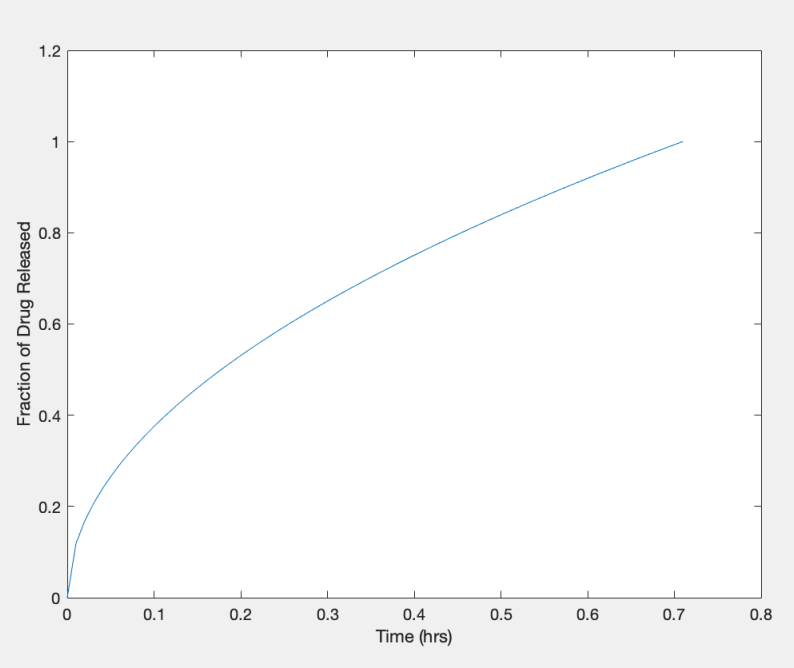

Figure 7. Release profile of 5 mg of uncoated glipizide in tablet form. It takes less than one hour to release nearly all of the drug from the tablet.

Packaging

The three types of beads will be packaged in a hard gelatin capsule (the same capsule type that is used by Ritalin LA), with a standard capsule size 1. Figure 8 depicts the final drug packaging and contents of the pill.

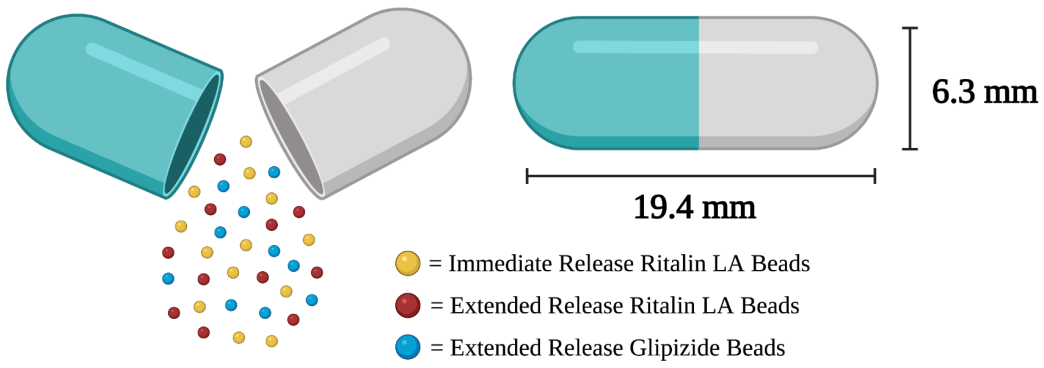

Figure 8. The contents of our pill will include immediate release methylphenidate hydrochloride beads (Ritalin LA formulation), extended release methylphenidate hydrochloride beads (Ritalin LA formulation), and extended release glipizide beads. The capsule will be a standard capsule size 1 with a length of 19.4 mm and a diameter of 6.3 mm.

Design Fabrication

Here we will discuss the process of fabricating our glipizide beads as well as coating them in our polymer. This protocol is based on a similar coated microbead formulation [95] utilizing Eudragit S-100 to deliver naproxen sodium to the colon. The fabrication process can also be seen below in Figures 9 and 10.

Glipizide Bead Formation. Glipizide will be mixed into a warm sodium alginate solution at a 1:6 ratio. The mixture will then be emulsified in light liquid paraffin with 2% by volume Span 80, a surfactant. The mixture will be stirred at 400 rpm for 1 hour to form microdroplets. This solution will then be mixed with a 5% mass/volume mixture of calcium chloride added dropwise at a rate of 1 mL/min to promote cross-linking of the polymer to solidify the bead surface. Microbeads will then be filtered off with a 400 um filter, washed with petroleum, frozen for 10 hours, and desiccated for 12 hours to form the base microbead.

Bead Coating Process. Microbeads will then be mixed into a 2.5% weight/volume mixture of Eudragit S-100 in a 1:1 mixture of acetone and isopropyl alcohol. The mixture will then be again emulsified in light liquid paraffin with 2% by volume Span 80 at 400 rpm for three hours. By the end, all solvent should be evaporated. Microbeads will be filtered off with a 400 um filter, washed again with petroleum and dried in a desiccator for 24 hours.

Bead Addition. These microbeads can then be weighed out to ensure addition of the correct amount of glipizide and added to an unsealed size 1 gelatin capsule with length 19.4 mm that has been pre-loaded with immediate and delayed release methylphenidate microspheres. As stated previously, the dose of methylphenidate microspheres will be identical to that of the Ritalin LA formulation. The gel capsule is then sealed and capable of being utilized for solution administration.

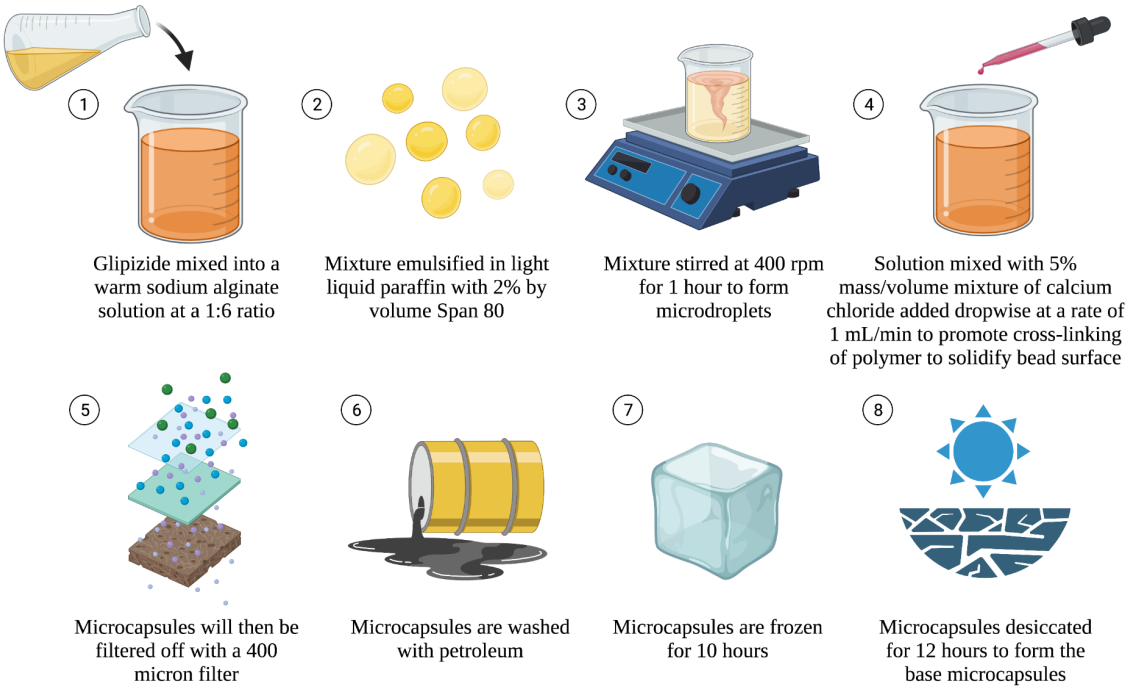

Figure 9. The first stage of the glipizide bead fabrication process involves mixing glipizide with sodium alginate (a coagulant) at a 1:6 ratio, emulsifying the mixture with paraffin to form microdroplets, and mixing with calcium chloride to solidify the beads.

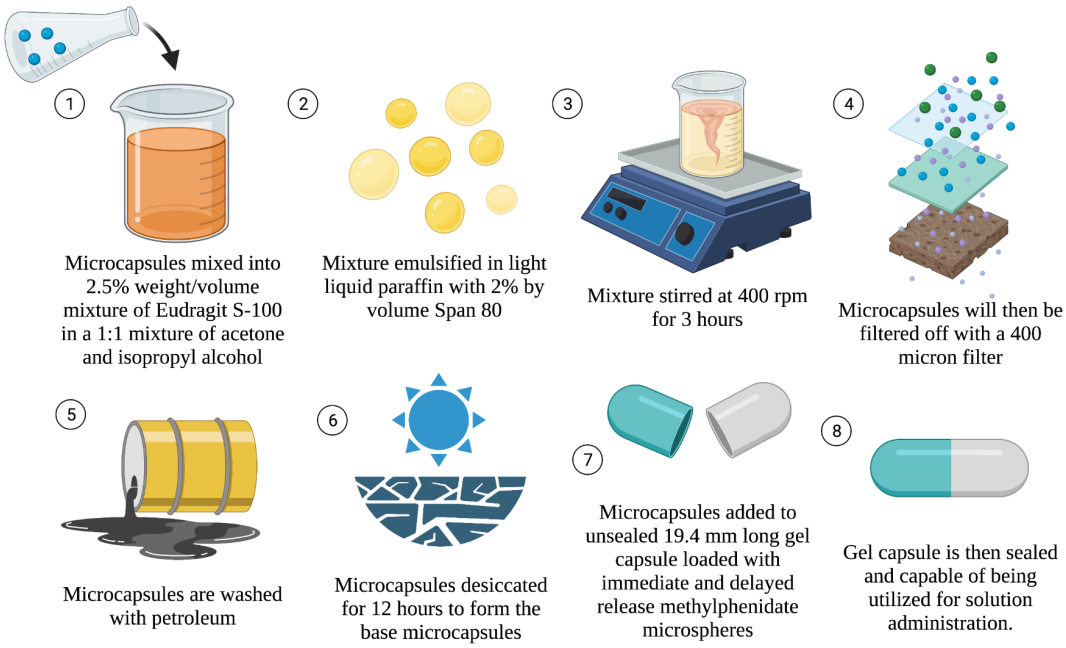

Figure 10. The second stage of the glipizide bead fabrication process involves mixing glipizide with a 2.5% weight/volume mixture of Eudragit S-100 to fully coat the beads, emulsifying the mixture with paraffin again, filtering the microbeads, and sealing them in a standard capsule size 1 with both immediate and delayed release methylphenidate beads.

Design Justification

In this section we will discuss the justification for each of our design choices.

ADHD Stimulant

First, our team needed to select an ADHD stimulant to utilize in our novel solution. In order to select an appropriate stimulant, we utilized literature to identify common ADHD stimulant medications that demonstrated a bimodal plasma concentration-time profile to prevent our team from needing to significantly alter the pharmacodynamics in our solution to ensure a reduction in medication effects compatible with the effect of an appetite stimulant.

Methylphenidate. Before selecting a specific drug, we first selected a category of stimulant medication. The most common and effective medications used for treating ADHD are methylphenidate and amphetamines [96]; however, wanting to maximize the potential impact of our design, we chose to focus on methylphenidate-based drugs as they tend to produce more side effects in adults than amphetamine-based drugs [16] and are also the most commonly prescribed drug class for patients with ADHD [97].

Ritalin LA. Difficulties in administering methylphenidate multiple times a day has been alleviated by the development of extended-release options that act over 8-12 hours [98]. These types of methylphenidates are intended to demonstrate a rapid initial increase in drug concentration after administering the medication, facilitate a decrease in plasma concentration around the hours of lunchtime to promote eating, increase plasma concentration again after lunchtime to control symptoms in the afternoon hours, and finally decrease plasma concentration in the evening to promote a normal appetite for dinner [88]. Our

team chose Ritalin LA as it shows more rapid initial absorption and significantly higher peak plasma concentrations as compared to other long-acting methylphenidate drugs [89]. Most importantly, Ritalin LA produces a distinct bimodal plasma concentration-time profile, with the plasma concentration falling about 3 hours after administration, or around the hours of lunchtime. This decrease in drug concentration is only seen in Ritalin LA compared to other long-acting formulations [90].

Conclusions. Our team has selected Ritalin LA due to its consistent bimodal plasma concentration-time profile which demonstrates a decrease in drug concentration three hours after administration. This decrease in drug concentration, paired with the release of our appetite stimulant, will allow for our team to meet several of our critical design specifications. Firstly, the Ritalin LA element of our design will be non-harmful, as this drug has already been tested and approved by the FDA as a substance that does not cause adverse drug events in more than 1 percent of cases. Secondly, we will not be reducing the effectiveness of ADHD treatment, as we are not altering the dosage or inhibiting the release of Ritalin LA. Thirdly, it will allow our solution to be personalizable as there are multiple dosing options with Ritalin LA. Finally, it will satisfy our stability requirement as the pills will be protected in a pill bottle or case. Ritalin LA will also satisfy several non-critical design specifications. As it is delivered in pill form, the rate of patients reporting difficulty with administration will not be greater than 15 percent, as typically 15 percent or less of patients report difficulty with pill ingestion. Furthermore, pills are portable and quick to administer.

Appetite Stimulant Dose

We will be using glipizide as our appetite stimulant (see Table 1 for comparison of appetite stimulant medications and justification of our choice of glipizide). Glipizide is typically prescribed at 5 mg [49] to be taken 30 minutes before a meal in otherwise healthy type 2 diabetes patients. To avoid any unexpected effects in patients who may experience abnormal insulin regulation, our team has narrowed our target market to be adult ADHD patients who do not have diabetes; because the target patient is now expected to have normal blood sugar control and insulin regulation, it is expected that this dosage should be high enough to induce insulin production, lower blood sugar, and induce hunger. As the dosage is intended to supplement consumption of one meal, it is expected that consumption of one full meal will satiate hunger. This matches the requirements of reducing the impact of appetite suppression by making eating lunch feasible while also limiting residual effects on hunger during the later half of the day, preventing overeating.

Drug Delivery Technology

Before our team was able to select an enteric polymer with which to coat our drug, we had to choose the drug delivery technology; however, choosing the means of drug delivery requires an understanding of how enteric polymers function in the gastric environment. More specifically, we researched the implications enteric polymer properties have on both enteric beads and enteric coated tablets.

Principle of Operation. Enteric polymers are intended to prevent drug dissolution in the stomach, allowing the drug to be absorbed in the intestinal tract. Glipizide is a lipophilic drug [99] and as a result diffuses passively from the lumen of the small intestine into the bloodstream.

Dissolution Properties. Enteric polymers undergo transformation in the gastric environment, rather than acting as an inert substance. The longer an enteric polymer resides in the acidic stomach, the more resistant the polymer becomes to dissolution in neutral intestinal fluid. Increasing resistance to dissolution means that dissolution may occur less than desired in the gastrointestinal tract, reducing the efficacy of our drug delivery system [100]. Therefore, it is vital that we select a drug delivery system that optimizes the timing of bead or tablet release from the stomach.

Enteric beads. One of the functions of the stomach is to reduce larger materials to sub-millimeter particles. If our team were to utilize enteric beads, once these beads enter the stomach, they are typically already below this size threshold and don't require size reduction. As a result, individual beads can begin exiting the stomach almost immediately after the dose is administered. This system offers many advantages for patients: first, with immediate release of the beads from the stomach, the drug can start being absorbed very quickly after dose administration; secondly, this mechanism is known to show low day-to-day variability for patients [100]. Finally, as the drug dosage is delivered in many subunits, failure of one subunit will not automatically result in failure of the whole dosage [101].

Enteric coated tablets. Compared to enteric beads, enteric coated tablets are typically much larger than the sub-millimeter threshold for particles exiting the stomach. This is immediately disadvantageous as the stomach will futilely attempt to reduce the size of the tablet once it enters the stomach, prolonging the time before the drug can be absorbed in the gastrointestinal tract. Furthermore, a tablet is a single drug delivery unit with uniform dissolution properties throughout the tablet coating. As a result, with an enteric coated tablet, a drug may be absorbed as intended or may pass through the entire intestinal tract without being absorbed, which makes day-to-day variability of drug delivery very high [100].

Conclusions. Ultimately, our team determined that enteric beads will allow for more rapid absorption of our ADHD stimulant medication after administration; furthermore, the release profile of both our ADHD stimulant and appetite stimulant will be more consistent day-to-day. Our decision to use enteric beads also complements our decision to use Ritalin LA, which utilizes Spheroidal Oral Drug Absorption System (SODAS) technology. Benefits of SODAS technology are well known; it offers inherent flexibility that enables customized dosages, controlled absorption, suitability for use with more than one active drug, as well as the other advantages offered by bead technology discussed in the *Enteric Beads* section [102].

Polymer Coating

In selecting which polymer coating to use for glipizide, our added appetite stimulant, the most important factor to consider was the timing of release. Our means of selecting a polymer coating will be discussed in this section.

Timing of Glipizide Release. As discussed previously in the *Ritalin LA* section, there is a distinct decrease in the ADHD stimulant concentration three hours after drug administration. Our team wanted to pair this decrease with an added appetite stimulant to stimulate a normal appetite. Assuming patients take our solution at breakfast, appetite stimulation would be desired approximately 4 hours later. This closely matches the period of lowest intradose methylphenidate concentration. To ensure appetite stimulation by this time point, we intend to begin glipizide release 3 hours after ingestion for it to be released over one hour.

In order to determine where in the gastrointestinal tract our appetite stimulant would need to be released, we researched the transit times in all gastrointestinal tract components to figure out ideally where beads would be located following drug administration. This information is included in Table 5.

Table 5. Cumulative transit time in the gastrointestinal tract by compartment, with associated pH. As transit proceeds, pH gradually rises, allowing for the utilization of enteric coatings that dissolve at higher alkalinity to delay release and absorption of medications. For a medication requiring release after 4 hours, a target release pH of ~7 is needed. Adapted from [93].

Compartment	pH	Cumulative Transit Time (hr)
Stomach	1.3	0.25
Duodenum	6.0	0.51
Jejunum 1	6.2	1.46
Jejunum 1	6.4	2.22
Ileum 1	6.6	2.81
Ileum 2	6.9	3.24
Ileum 3	7.4	3.55

As seen in Table 5, there is a cumulative transit time of 3.24 hours (approximately 3 hours and 14 minutes) before our drug will reach the third compartment of the ileum, making this segment of the gastrointestinal tract ideal for release of our appetite stimulant.

Breakdown of Polymer. As seen in Table 5, the pH of the third compartment of the ileum is approximately 7.4; therefore, our team determined that we must coat the glipizide bead in a polymer that will degrade at this specific pH. Methyl-methacrylate derivatives are commonly used as enteric coatings on account of the tunability of their dissociation pH [103]. The ratio of carboxyl groups to ester groups added determines the pH, with a 1 to 1 ratio used in the polymer Eudragit L, which solubilizes at a pH of 6, and a 1 to 2 ratio in used Eudragit S, which solubilizes at/above a pH of 7 [103]. As pH increases to 7.4 in the third compartment of the ileum, we chose to utilize Eudragit S as our microbead coating. Specifically, we will use Eudragit S-100, which is commonly used for enteric coatings. The release of a drug coated in Eudragit S-100 as pH is varied can be seen in Figure 11.

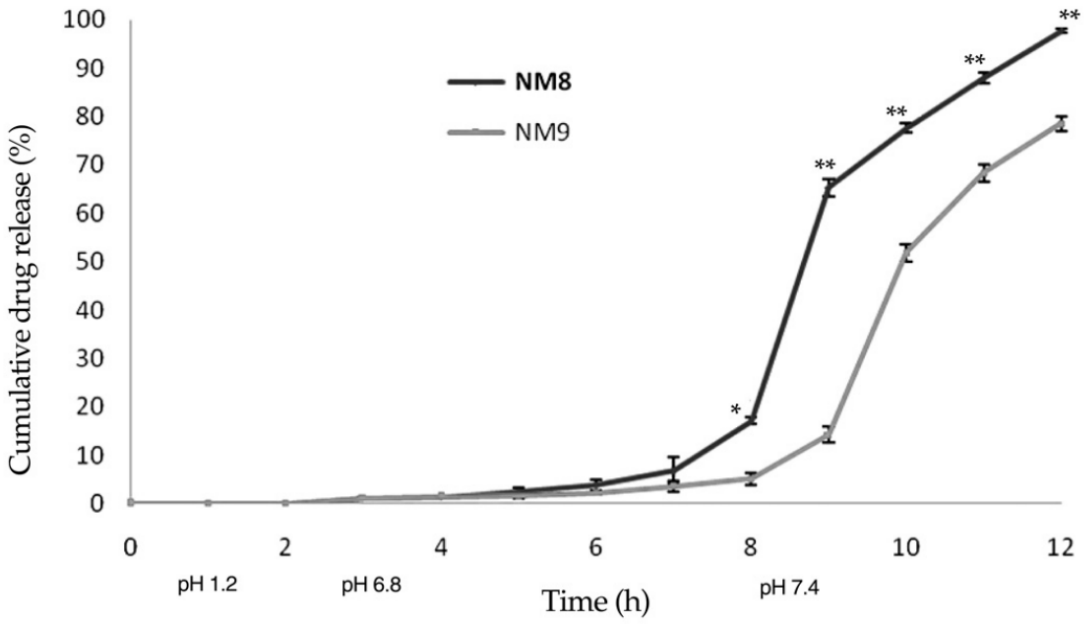

Figure 11. Release of a drug coated in Eudragit S-100 as pH is varied. At low pH there was very little release of the drug as Eudragit S was unable to break down at low pH. Once the pH reached 7, the Eudragit coating was broken down and the drug was released. NM8 represents a thinner Eudragit coating than NM9, demonstrating that thinner coatings result in more rapid drug release.

Particle Sizing. Our glipizide microbeads will be smaller than 800 μm in diameter. Microparticles smaller than 800 μm can pass through the stomach valve leading to the small intestine without the need for gastric emptying, and thus does not require the patient to eat at a specific time for the drug to be effective [101]. To determine the exact size of the particle, we plan to model the release rate of our glipizide microbead with varying radii and determine which release profile most closely matches the release rate of traditional glipizide. We plan to use the Hopfenberg model, which describes the drug release for surface-eroding microbeads [104]. The Hopfenberg model (described further in the Verification and Validation section) relates fraction of drug released to the radius, initial drug concentration, time, and erosion constant.

Coating Thickness. The thinnest coating possible will achieve rapid drug release in the ileum. Eudragit S-100 exhibits a surface-erosion mechanism [105], thus the largest rate of polymer degradation occurs at the beginning of dissolution [106]. Thinner coatings will therefore take less time to degrade and initiate drug release. In a study comparing the drug release profiles of microbeads coated in various thicknesses of Eudragit S-100, the core:coat ratio of 1:2.5 (NM8) exhibited a significantly faster cumulative drug release than the ratio of 1:5 (NM9) (see Figure 11) [95]. Further, there is almost no observed degradation of the Eudragit S coating below a pH of 7, even for thin coatings [95]. To achieve the thinnest coating possible, we will modify the polymer concentration in solution during our fabrication process. Studies comparing Eudragit coating thicknesses and concentration of polymer in solution show that increasing the % weight/volume of polymer in solution increases the coating thickness (see Figure 12 below) [107]. Therefore, we will use the lowest concentration possible to achieve the thinnest coatings possible on our microbeads. Currently, the lowest concentration commonly used in practice is 2.5% polymer w/v [107], so that is the concentration we will utilize in our fabrication process.

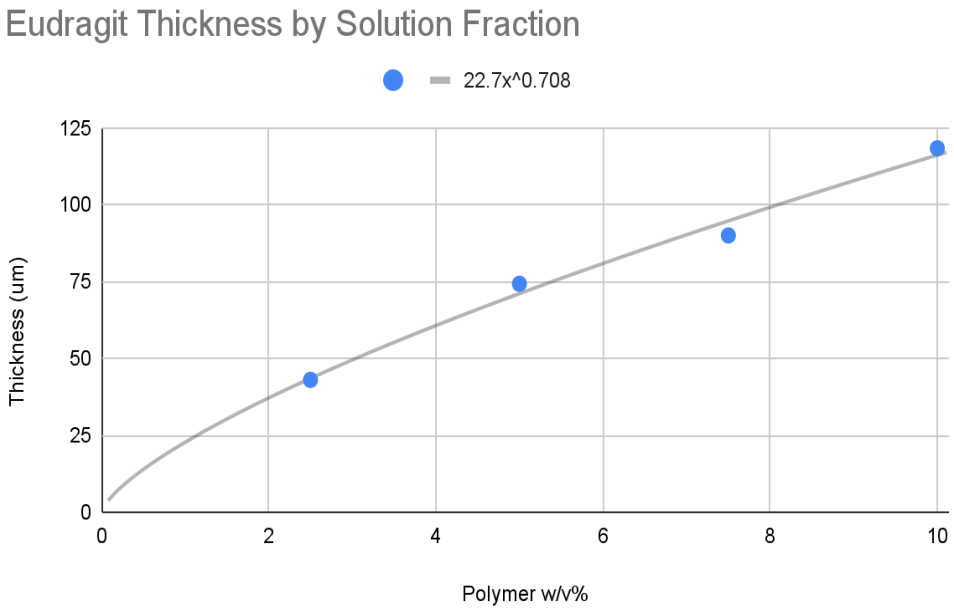

Figure 12. Eudragit coating thickness versus polymer concentration in solution shows a positively correlated relationship and can be described using a power function $Y= 22.7X^{(0.708)}$. Smaller polymer concentrations yield thinner Eudragit coatings.

Capsule Sizing

Ritalin LA currently uses standard capsule size 2 (18.0 mm in length, 370 mm^3 in volume [108]) to deliver the 20 mg of MPH [91]. We plan to add 5 mg of glipizide to our capsule, which has a density of 1.34 g/cm^3, and thus will require roughly 3.73 mm^3 of additional space within the capsule. Therefore, we plan to increase the capsule size to capsule size 1 (19.4 mm in length, 500 mm^3 in volume) to accommodate for this slight increase in volume. The use of larger capsule size can also accommodate increases in doses of either MPH or glipizide.

Failure Modes and Effects Analysis

We conducted a failure modes and effects analysis (FMEA) in order to determine potential hazards associated with our solution, the severity and frequency of those hazards, and to produce ways to mitigate or remedy those hazards.

Search methods

Our analysis of these failure modes was informed by literature searches primarily conducted on PubMed, as well as information supplied by Micromedex. Some key PubMed search phrases included *misplaced pill bottle*, *pill bottle design*, *hard gelatin capsule dissolution*, *ADHD forgetfulness*, *methylphenidate release*, *glipizide release, enteric-coated microbeads, difficulty swallowing pills,* and *breaking pills.* In order to find the most relevant information, we also used Boolean operators to further refine our search terms. Our findings primarily gave us insight into how the design of pill containers influences a patient's ability to locate them, the way a hard gelatin capsule and enteric-coated microbeads would behave if left in the mouth for longer than it takes to swallow, and the potential outcomes of people having trouble administering pills. Micromedex specifically supplied information on Ritalin LA, linking to the full label which addresses that users should not chew Ritalin LA capsules [87], and thus inspired our third failure mode.

FMEA Ratings

Our failure modes are each rated according to the severity of the outcomes and the frequency at which these failures may occur. The rating system used for both is a scale of 1-5, with 1 being low and 5 being high. Specifically, a severity of 1 correlates to a nuisance or something that simply would need to be redone, 2 is minor injury or damage, 3 is moderate injury at the level of a finger fracture, 4 is reversible major injury, and 5 is irreversible major injury or death. For frequency, a rating of 1 means the failure mode is rare, 2 is occasional, 3 is medium, 4 is often, and 5 is frequent or nearly guaranteed. The benefit of this rating system is that multiplying a given hazard's severity and frequency ratings together produces a risk priority number (RPN) that can be used by an engineering team to determine a hazard's overall risk and thus how important it is to address that failure mode before finalizing the design.

Table 6. This table summarizes the main hazards associated with the design of our solution, as well as our proposed remedies. Failure modes were primarily identified within the task of the patient administering the pill.

Failure Mode	Failure Mode Cause	Severity	Frequency	RPN	Remedy
Patient loses or misplaces pill bottle	Container is too small, the color does not stand out, or the pill bottle is left in an unintended location.	1	4	4	Design a pill bottle with a brightly colored cap for it to be more easily spotted by the patient. Alternatively, design a pill bottle with the ability to emit a sound when the patient misplaces it using a bluetooth connection between the pill bottle and the patient's phone.
Patient puts pill in	Patient forgets	1	4	4	Encase the microbeads in a

their mouth without having water nearby to aid in swallowing.	to have water close by when they take their pill.				hard gelatin capsule to prevent early release of the drug in the mouth. Hard gelatin capsules take up to two minutes to fully dissolve at body temperature [109], giving the patient this amount of time to get water.
Patient opens up the pill to take their medication. Sprinkling capsule contents over food allows patients to chew and potentially fracture enteric coating, resulting in immediate drug release.	The slightly larger pill size due to additional microbeads increases the difficulty patients have ingesting the pill [38].	1	2	2	Offer an alternative formulation in which the patient takes two size 3 tablets rather than one size 1 tablet. Size 3 tablets are smaller and about half of the volume of one size 1 tablets [110]

Discussion of failure modes

Acui-Care identified three main failure modes associated with our solution, all within the task of the patient administering the pill. These failure modes are that the pill bottle may be temporarily lost or misplaced, the patient may put the pill in their mouth without having water close by, and the patient breaks open the pill, sprinkles the contents over food, and chews the contents of the pill. The discussion of these hazards, their severity and frequency, and their potential remedies are included in this section.

Patient loses or misplaces pill bottle. One potential hazard that Acui-Care has identified in our design is the patient misplacement of the medication container. This would primarily occur if the size or color of the container does not make it stand out or be easily noticed, or if the container was left in an unintended or atypical location. The severity of this hazard is low as it only causes the patient to be unable to take their medication, resulting in no ADHD symptom relief until the medication container is located. Since this is a nuisance to the patient but would not cause them any harm, this failure mode has been given a severity rating of 1. Given that people frequently misplace objects such as keys, phones, and other commonly used items, as well as the fact that forgetfulness is a symptom of ADHD, we have ranked this failure mode with a frequency rating of 4, giving an overall RPN of 4.

Some remedies for this failure mode that Acui-Care could implement involve the design of a container for our solution with features to make it easier to find in the event of a misplacement. The first design choice would be a brightly colored cap to make it easier for the patient to locate the bottle. Another design choice would be designing the bottle such that it has the ability to emit a sound when misplaced; this feature could be controlled through a bluetooth connection between the pill container and the patient's cell phone.

Patient takes pill without having water close by. The second failure mode we have identified is that the patient may put the pill in their mouth without having water close by to aid in swallowing. The cause of this failure mode is forgetfulness, as the patient may forget to have water close by when they are taking their medication or they may forget to refill their water glass that they have on hand. We determined this to be a level 1 in severity, corresponding to a nuisance, as allowing the pill to reside in the mouth may

result in dissolution of the pill's coating and release of the immediate-release MPH in the mouth. Early release of the drug in the mouth will result in reduced ADHD symptom relief, particularly in the first half of the day. Reduced symptom relief will be a nuisance to the patient but should not cause them injury. We determined this failure mode to be a level 4 in frequency, as this is a commonly observed error in the personal experience of both our team members and the reviewers of our design presentation, resulting in an overall RPN of 4.

Acui-Care's remedy for this failure mode is to encase the microbeads in a hard gelatin capsule to prevent early release of the drug in the mouth. Upon reviewing literature about the dissolution of various capsule shells, we found that hard gelatin capsules take up to two minutes to fully dissolve at body temperature, giving the patient this amount of time to get water [109].

Patient breaks open pill and sprinkles contents over food. The third failure mode Acui-Care has identified is that chewing our solution may result in immediate drug release, rather than the intended extended release. This could occur if a patient struggles to swallow our solution's size 1 capsule, which is one size larger than the capsule currently used for Ritalin LA. A patient who struggles to swallow a pill may choose to open up the capsule and sprinkle the contents onto food to make ingestion of their medicine easier. However, this opens up the possibility of chewing the microbeads which could potentially fracture their enteric coating. A fractured enteric-coated microbead will not show the expected and desired delayed release profile, and thus the patient's dose of glipizide will not be timed properly. We determined this to be a level 1 in severity, as the effects of this failure mode will be a nuisance to the patient, but should not cause them injury. The immediate and extended release methylphenidate will be released immediately, resulting in more ADHD stimulant (and as a result more severe adverse effects such as nausea, insomnia, irritability, etc). Furthermore, if the extended-release MPH is released early, then the patient will likely experience more severe ADHD symptoms in the afternoon. We also ranked this failure mode to be a 2 in frequency, as our research suggests that only 15-20% of people on average have difficulty administering pills [6], thus giving an RPN of 2.

Our team's remedy for this failure mode is to offer an alternative formulation of our solution in which the patient takes two size 3 tablets instead of one size 1 tablet. Since size 3 tablets are about half the volume of size 1 tablets [110], this should make ingestion of our solution easier and thus breaking open the capsules will be unnecessary.

VI. COST ANALYSIS

Current and Projected Costs

In this section we will discuss the current patient costs associated with Ritalin LA, the manufacturing cost of our solution, and the patient cost of our solution. It is important to note that these values are rough estimations, as healthcare and prescription costs can be highly variable based on a patient's location and insurance. Additionally, we would expect the cost of the raw materials of our drug to decrease during the actual production process as they would be bought in bulk.

Patient Cost of Ritalin LA

To be prescribed Ritalin LA, a patient must first visit a healthcare provider. This process would take a minimum of 1-2 visits, depending on the patient's condition. A visit to a psychiatrist is estimated to be $100-200, with the initial visit ranging from $300-500 [111]. After the provider prescribes Ritalin LA to the patient, the patient pays up to $364 for one month's prescription of Ritalin LA [112].

Cost of Manufacturing our Solution

The fabrication method we described in our Design Outputs section is ideal for small-scale production of our microbeads, and utilizes beakers, stir-plates, and other laboratory equipment. However, we will need to use a large-scale production facility to actually manufacture our product. To best estimate the manufacturing costs, we will estimate the cost of production of Ritalin LA, as this process also requires microbead formation and coating, and bead combination into the capsule.

Ritalin LA is produced by Recro Pharmaceuticals, a drug development and manufacturing company [113]. Recro Pharmaceuticals estimates their manufacturing costs for one year to be $38-43 million, with this value including labor, materials (including packaging), and operating expenses [114]. As Ritalin LA is one of three of their largest products [114], the cost of manufacturing Ritalin LA is roughly ⅓ of Recro's total manufacturing cost, or $12.66-14.33 million per year. Though this may seem like a large manufacturing cost, the sales of Ritalin LA are over $21 million per year [115], with this number expected to grow as ADHD diagnoses and prescriptions continue to increase [17]. Additionally, we acknowledge that this estimate does not include the upfront cost of the facilities or production equipment, however we intend to outsource the manufacturing, like Ritalin LA currently does.

Patient Cost of our Solution

Our product consists of our proprietary glipizide microbeads as well as the current formulation of Ritalin LA (20 mg). Wholesale Ritalin LA is estimated to cost $165 for one month's supply [116], and includes the immediate and extended release methylphenidate microbeads and the drug capsule. Though we will be using a slightly larger drug capsule, we will also be using a hard gelatin capsule, and therefore we estimate the cost to be roughly the same.

Next, we will include a total of 5 mg of glipizide in each capsule. One month's supply of glipizide (5mg daily) is roughly $450 [117]. We expect this to be an overestimation as it is the prescription form of glipizide. We would buy the raw product in bulk so we could add it to our formulation.

We will also require 18.56 mg of LMP per capsule and 7.96 mg of HPMC per capsule to hold our drug core together (see Appendix B for calculations). LMP costs roughly $16.30 per kilogram [118], and therefore would cost roughly $0.0003 per capsule and $0.009 per month supply. HPMC costs roughly

$4.12 per kilogram [119], and would cost roughly $0.00003 per capsule and $0.00098 per month supply. (We will discuss why we switched to HPMC and LMP in the Verification and Validation section.)

Lastly, our Eudragit S-100 coating has a total weight of .045 grams per capsule, given a coating thickness of roughly 43 microns (see Appendix B for calculations). Eudragit costs roughly $434 per kilogram [120], and thus would cost $0.02 per capsule and $0.59 per month supply.

Adding the costs for our product gives us a total wholesale price of $615.59 Again, this estimate is likely inflated from our glipizide value, as we could only find the wholesale price of glipizide in pill form. Ideally, we would be purchasing glipizide in powder form in bulk, not in individualized packaging.

Discussion

Though the cost of our product is more expensive than traditional Ritalin LA, we believe that patients will find the greater tolerability of our product worth the additional price. Our stakeholder even informed us that she would pay up to double the cost of her current medication for a solution that does not suppress her appetite. However, in the event that the cost of our product is a barrier for some patients, we could reduce the patient cost by purchasing as much of our materials in bulk, and choosing a manufacturing company with the lowest operating costs. Additionally, we could work with insurance companies to offer patients a reduced cost option.

As we discussed in our User Needs section, the effects of long-term appetite suppression are numerous and deleterious to a patient's health. The CDC states that insufficient quantities of food (and nutrition) can lead to many chronic conditions [121]. The cost of these conditions are quite large and variable, but people with decreased food and nutrient intake have an average of 11% greater healthcare costs than those with healthy food intake levels [121]. Therefore, for patients who experience the effects of appetite suppression due to their methylphenidate stimulant, the use of our product could prevent the onset or severity of chronic conditions and ultimately prevent the increase in healthcare costs. Additionally, by improving the patient's food and nutrient intake, it could increase the patient's work performance, leading to greater productivity and less work time lost due to the patient's condition.

VII. VERIFICATION AND VALIDATION

Design Updates

Before we describe our team's physical and paper testing plans, we would like to update the management team about changes to our design since our External Design Review. First, we have decided to alter the composition of the glipizide microbead core to a matrix of glipizide, hydroxypropylmethylcellulose (HPMC), and low methoxyl pectin (LMP). HPMC and LMP are replacing sodium alginate, the material we originally planned to use in the core of the microbead. HPMC and LMP serve the same function of coagulating and binding the glipizide core but are more well-documented in literature in terms of their use as microbead matrix materials [122]. We have updated the fabrication process in our Design Outputs report and will include the finalized version in our DHF.

Physical Testing Plan: Drug Release Modeling with the Hopfenberg Model

In this section we will discuss our use of engineering software to provide in-depth, quantitative analyses of at least two design features or requirements previously approved by managers. For our physical testing, we will be using a model that will simulate the release of glipizide from an enteric microbead with the Hopfenberg model. With this model, our team will be able to identify the optimal microbead radius as well as the optimal drug concentration within the microbead that will most closely match the release profile of traditional glipizide drug release. The purpose of this test is to determine whether the release of glipizide, as modeled with our program, will satisfy the design requirement of reducing the impact of appetite suppression. Success will be indicated by successful release of 5 mg of glipizide within one hour after the dissolution of the enteric coating.

Modeling Setup

In this section, we will discuss the setup of the model, including the softwares used, the assumptions of the model, the geometries and equations used, and values obtained from literature review.

Softwares Used. For our model, we used MATLAB, a programming language and numeric computing environment that can be used to plot functions and data. The code used for our MATLAB model is included in Appendix C.

Model Assumptions. The first assumption of our model is that drug release and drug absorption occur simultaneously. In the body, there will be some transit time as the drug diffuses from the lumen of the small intestine, across the epithelium, and into the blood. In contrast, our model assumes that the drug goes immediately from the microbead core into the blood with no transit or absorption time across the epithelium; in other words, drug release and drug absorption are simultaneous processes. This affects our model by simplifying it; if we were to model drug absorption in addition to drug release, we would need to account for the release of our drug using the Hopfenberg model and the diffusion of the drug into the blood. Since diffusion occurs rapidly compared to release, it is appropriate to exclude from our model.

The next assumption of our model is that no drug will be released prior to the complete dissolution of the enteric coating. In reality, the enteric coating might not dissolve uniformly, resulting in drug release from some parts of the microbead before others; however, we are assuming that no drug is able to be released from the core before the core is completely exposed. This affects our model by allowing us to utilize the Hopfenberg model because release will occur uniformly from a spherical shape rather than inconsistently from an irregular shape. Furthermore, if we excluded this assumption, the release time would only decrease, as drug release would begin earlier. Therefore, by including this assumption, we are finding the

maximum time needed for complete drug release. The moment when enteric dissolution is complete and drug release begins marks t = 0 in our model.

Geometries and Equations Used. The Hopfenberg model describes "dissolution, swelling, and polymer chain scission as a final zero-order process" [123]. We know that glipizide and HPMC/LMP (the contents of our delayed release glipizide microbead core) follow matrix erosion [124], meaning that the outer surface of the matrix becomes hydrated (due to water absorption from the hydrophilic polymers), forming an outer gel layer. After the outer layer is hydrated, the polymeric chains begin to dissolve and the bead will erode. Therefore, as the microbeads undergo dissolution, swelling, and polymer chain scission as well as follow zero order kinetics [125], we know our combination of materials will be accurately described by the Hopfenberg model.

We will utilize the Hopfenberg model (see Equation 1) [126] to determine the optimal radius and initial concentration of our extended-release glipizide microbeads. The Hopfenberg model relates time *t*, radius R, erosion rate $k_{ero,\,0}$, and initial concentration of drug C_0 to the fraction of drug released M_t / M_∞ from spherical microbeads. We will modify the concentration and radius values to ensure that glipizide is fully released within one hour (assuming the enteric coating is fully dissolved prior to the start of drug release), mimicking the release rate profile of 5mg of traditional glipizide in tablet form.

$$\frac{M_t}{M_\infty} = 1 - \left[1 - \frac{k_{\text{ero},0} t}{C_0 R}\right]^3 \qquad (1)$$

Values from Literature. The most important value that we needed to obtain was the surface erosion rate constant (k_{ero}), a value that describes how much drug erodes from some amount of surface area over time. This value was necessary for the Hopfenberg equation (see Equation 1). Our team was unable to find a value in literature for the erosion rate constant of HPMC and LMP with proper units for the Hopfenberg equation, so we calculated this value based on data found in a report on the development and in vitro characterization of microbeads for prolonged drug release [122]. A complete summary of how this constant was calculated is included in Appendix C. The report included data on the size, drug content, and polymer combination of each formulation tested in their experiment. We chose the formulation that included a 7:3 ratio of LMP to HPMC as this formulation had the highest amount of HPMC. A higher HPMC content was important as we found in literature that HPMC closely follows the Hopfenberg model [127].

To calculate k_{ero} , we needed to know the initial radius of the microbead, the initial concentration of drug inside the bead, and the time necessary to release all of the drug. We used a radius of 480.44 μm, as this was directly given in literature. To calculate the initial drug concentration, we had to calculate the amount of drug inside each individual bead. The report gave that the drug content of 100 mg of microbeads was 15.74 mg. We used the densities of LMP (1.81×10^{-9} mg/μm^3), HPMC (1.39×10^{-9} mg/μm^3), and glipizide (1.3×10^{-9} mg/μm^3) and their relative amounts (7:3 ratio of LMP to HPMC and an 85:15 ratio of polymer to drug) to calculate the overall density of the core: (1.624×10^{-9} mg/μm^3).

$$Average\ Density = \frac{(Substance\ A\ Density * \%\ Substance\ A) + (Substance\ B\ Density * \%\ Substance\ B) + \cdots}{100} \qquad (2)$$

Using the radius to calculate the volume of the beads, we calculated the mass of an individual microbead and then divided 100 mg of microbeads by the microbead mass to obtain the total number of microbeads.

$$Mass = Density * Volume$$

(3)

Next, we divided the total drug content by the number of microbeads to get the drug content in each microbead. Finally, we divided the drug content in each bead by the bead volume to obtain the initial drug concentration in each microbead. The value obtained for drug concentration was 2.55×10^{-10} mg/μm^3.

$$Drug\ concentration = \frac{\frac{Total\ drug\ content}{\#\ of\ microbeads}}{Volume} \qquad (4)$$

To find the time necessary to release all of the drug, we analyzed a figure that showed the percent of drug released over time (Figure 1). We found that the drug would be released entirely in approximately 7 hours. After rearranging the Hopfenberg equation (1) We used these values to calculate k_{ero}, which was utilized in our model.

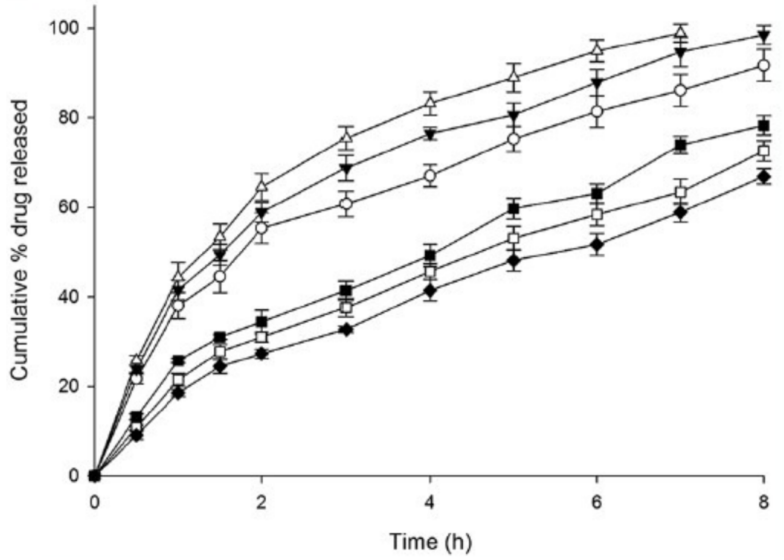

Figure 1. In a study on mucoadhesive microbead formulation for prolonged drug release, a radius of 480.44 μm resulted in complete drug release in 7 hours. This time was used to calculate the erosion rate constant for our Hopfenberg model.

In addition to finding k_{ero}, we used the literature to determine the bounds for our values for R and C_0. We know that microbeads smaller than 800μm in diameter ($R \leq 400$μm) can pass through the stomach valves without the need for gastric emptying [128], meaning that the patient wouldn't have to time their pill consumption with food consumption. Considering our enteric coating will have a thickness of approximately 40μm, the upper bound of our radius should be 360μm. Additionally, in a study utilizing a fabrication method similar to ours to create drug-loaded microbeads, the researchers produced an average size microbead radius of roughly 100 μm with a standard deviation of 5μm [129]. (This was the smallest average size we could find with this fabrication method.) Therefore, the lower bound we could produce with our fabrication method is about 90 μm (assuming a normal distribution of microbead sizes). Thus we will want to model our microbead radii as between 90 and 360 μm.

Next, we know that C_0 is a measure of the amount of drug present in the polymer matrix. As we can add any amount of glipizide to our combination of polymers, there are essentially no bounds to the concentration we could create in our microbead core matrix, aside from approaching a matrix composition

of 100% glipizide, which is extremely unlikely given the current concentrations used in literature are in the range of 10^{-10} mg/μm^3 [122].

Testing Results

In this section we will discuss the results of our physical testing. Figure 2 shows the release profile of our glipizide microbead with two optimized design parameters: microsphere radius and initial drug concentration, the values of which will be discussed below. These results allow us to verify our requirement of reducing the impact of appetite suppression by ensuring drug release in one hour and thus stimulating appetite around lunchtime.

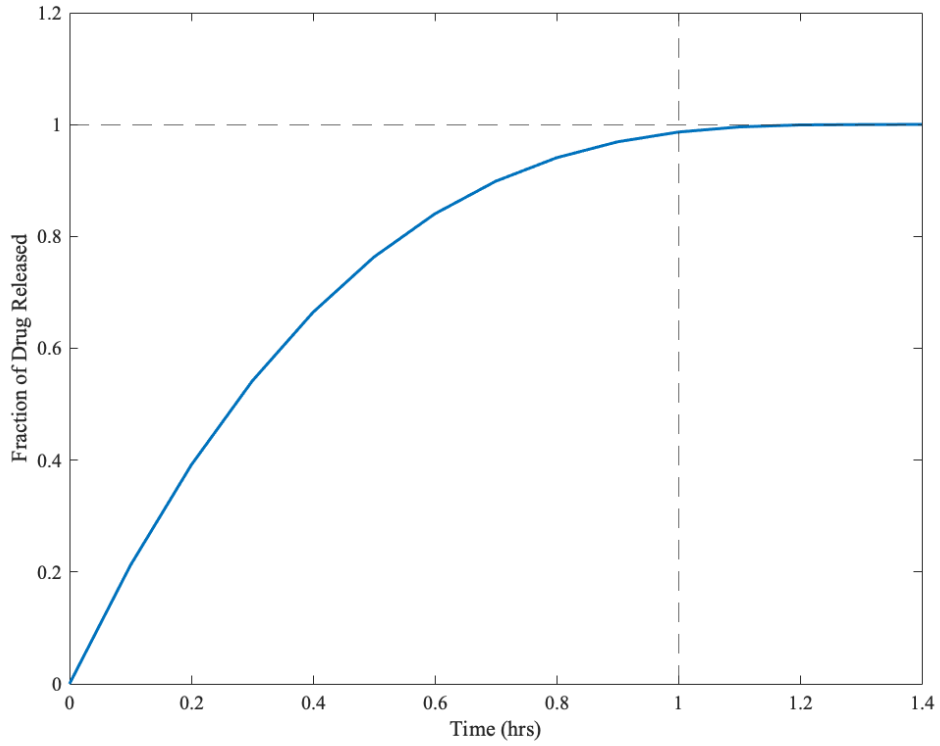

Figure 2. A radius of 90 μm and an initial concentration of 2.55x10^{-10} mg/μm^3 produces the following drug release profile. Nearly all of the drug is released in one hour, which matches the drug release profile of 5mg of glipizide in tablet form.

Initial Drug Concentration. With a practically unlimited range of potential initial drug concentrations, we decided to first use the same value that we found in our calculation of the erosion rate constant. If we found that the radius necessary to achieve our target release profile with this initial concentration was outside of the bounds discussed in the *Values from Literature* section, we planned to vary drug concentration. This was unnecessary as we found an in-range radius, which will be discussed in the next section.

Radius. After deciding on our initial drug concentration, we varied the radius to see which value most closely matched our desired release profile. Our team ultimately found that a radius of 90 μm allows for complete drug release in about one hour; additionally, it is within the feasible bounds for our microsphere radius, making it viable for our design.

Physical Testing Conclusions

As seen in Figure 2 above, we were able to obtain complete drug release in one hour with a microbead radius of 90 μm and an initial glipizide concentration of 2.55×10^{-10} mg/μm^3. By releasing the drug completely in one hour (and delaying drug release for roughly three hours), we are able to ensure a stimulated appetite around lunchtime, thus meeting our design requirement of reducing the impact of appetite suppression. (There is no need to stimulate appetite for breakfast or dinner as the Ritalin LA acts over only 8 hours, thus the patient will not feel the side effects of the drug during those mealtimes.)

The next steps for our physical testing include fabricating our microbeads (without a coating) with our theoretically determined drug concentration and radius, and conducting in vitro tests (in a solution with a pH of about 7 to represent the conditions of the ileum 2 and ileum 3) to measure the experimental drug release. These tests would confirm that our microbeads follow the drug release profile that we modeled and further ensure that our design requirement of reducing the impact of appetite suppression is being met by our design.

Paper Testing Plan: Utilizing a Clinical Trial to Validate Critical, Short-term Endpoints

In this section we will outline a clinical trial for our solution. This paper testing plan includes most of the sections required in a FDA clinical trial protocol for pharmaceuticals. Our clinical trial, as will be evident by what is derived from the endpoint data, is designed to enable a quantitative validation of the final design for the design inputs. This section will not discuss verification, as while we understand verification is an important part of the testing process, most of our specifications are based directly on patient response to our solution and thus would be difficult to approach through such means.

This plan describes a Phase 3 clinical trial. Phase 1 clinical trials are conducted to determine the optimal range of doses of a product for usage in humans and the overall pharmacological properties and phase 2 trials are used to further study efficacy and safety [130]. Meanwhile, Phase 3 trials continue to answer questions on safety while expanding the breadth of participants and answering questions on comparative treatment efficacy utilizing multiple control groups. Out of these phases, only the third is capable of validating our full set of design inputs effectively on account of its broader scope, longer time scale, and larger number of participants.

Both of the compounds of our solution, glipizide and extended release methylphenidate, have been approved for usage in humans under the brand names Glucotrol [131] and Ritalin LA [132]. Furthermore, pharmaceutical resources claim that there is no risk of adverse interactions [133]. With data existing on the safety and efficacy of these compounds, it made sense for us to focus our efforts on the design of a Phase 3 trial.

Clinical Trial Overview

ADHD patients that take stimulant medication, such as Ritalin LA, typically experience a variety of adverse side effects from their pharmaceutical treatment. Among these side effects, appetite suppression can have a significant impact on the patients; a failure to eat can lead to anemia, infertility, bone loss, poor dental health, and other health problems [27].

As requested by the management at Pure Chemistry, Acui-Care has developed a novel solution to reduce the impact of appetite suppression on ADHD patients taking Ritalin LA medication. The solution takes the form of a traditional pharmaceutical pill containing microbeads filled with methylphenidate and glipizide. While the methylphenidate acts as the stimulant component to address the ADHD side effects, glipizide can induce hunger by lowering blood sugar levels. Controlled time release, as determined by the properties of the enteric coating (see *Physical Testing Plan*), allows glipizide to be absorbed into the human body 3-4 hours after consumption of the pill. Patients may take our solution in the morning, and can experience physiological hunger induced by the glipizide component in the middle of their day. This encourages the patient to eat, reducing the impact of appetite suppression in the stimulant component.

The following sections will discuss the aims, endpoints, study design, and study plan for our trial.

Aims

In this trial, our explicit aims are focused on patient-level response to our solution. This is because they should map to endpoints (see *Endpoints*). Our trial has three primary aims, to:

1. Determine impact of solution on appetite suppression as compared to treatment with stimulants and stimulant-naive states
2. Determine effectiveness of solution for treatment of ADHD as compared to no treatment and treatment with stimulant medications

3. Determine severity of side effects of solution as compared to stimulant medications

These aims map back to our design requirements of reducing the impact of appetite suppression, not reducing the effectiveness of ADHD treatment, and not increase adverse effects experienced by patients over those implicit in current stimulant medications. These are the second through fourth most important requirements, as determined by the team and are directly measurable through quantitative metrics.

Our trial has one secondary aim, to:

1. Determine frequency of healthcare visits required to effectively utilize the solution as compared to utilizing stimulants alone

This aim relates to our requirement that the solution does not increase the number of visits required with a healthcare provider to properly utilize it.

Note that several requirements are not directly covered as study aims, namely safety of the product, adverse interactions with medications for comorbid conditions, and personalizability of the product. These requirements focus on the bulk properties of the patient population, meaning that the response of no individual patient may be representative of the overall population. Both safety-related requirements assume a small fraction of patients (< 0.5%) will be impacted and will be covered by the *Pretreatment Events and Adverse Events* section required for the clinical trial. In our statistical analysis, these types of adverse events will be focused on and directly compared to our corresponding specifications. Furthermore, our specification for personalizability is based on the fraction of patients for whom an effective dosage can be found. Patients who do not find such a dosage are able to voluntarily withdraw under the conditions that will be described in the *Criteria for Discontinuation or Withdrawal of a Subject* section required for a clinical trial. In our statistical analysis, the fraction of patients who disclose withdrawing for this reason will be compared to the overall patient population for determination of if the requirement is met.

Endpoints

Endpoints are quantitative measurements taken for each patient in the trial utilized to determine if the solution meets the aims. The requirements and specifications examined are from Table 1 of our Design Inputs. Specifically, the endpoints of the clinical trial will address the following short-term, critical requirements:

- Non-harmful
- Reduces impact of appetite suppression
- Does not reduce the impact of ADHD treatment
- Does not increase adverse effects experienced by patients
- Personalizable; the extended release medication must offer different dosing options
- Limits adverse interactions with medications commonly prescribed for comorbid conditions
- Does not increase frequency of healthcare visits

The primary and secondary endpoints described in this section indirectly address the first 4 listed requirements outlined above. All of these short-term critical requirements and how the clinical trial quantitatively addresses them are given in more detail in the *Statistical Methods* section.

In the design of clinical trials, one endpoint is generally selected as the primary endpoint and utilized to determine the necessary sample size for the study through a power analysis [134]. While the endpoint is measured along with all others during the trial, the unique characteristics of its response determine the

form of the power analysis. Our primary endpoint is changes to patient weight, utilized to determine the impact of the solution on appetite suppression. Originally, we sought to utilize Food Frequency Questionnaire responses as the primary endpoint, but the statistical test utilized (see *Statistical Methods*) is nonparametric and not thus conducive to a power analysis.

Our secondary endpoints are:

1. Responses to the Food Frequency Questionnaire
2. Score on the Conners Scale for ADHD Assessment
3. Score on the Conners Continuous Performance Test (CPT)
4. Score on the FIBSER Scale

Responses to the Food Frequency Questionnaire will be utilized as a secondary measure of the impact of appetite suppression on patients in the study. While we expect weight to provide insight into general trends in diet quantity, we intend to validate these results with FFQ results, providing richer insight into changes to diet [30].

The Conners Scale for ADHD Assessment [31] will be utilized as our primary metric for determining the effectiveness of our solution for treatment of ADHD. It is a comprehensive test[, requiring interviews with multiple stakeholders in a patient's life. While this makes the test more holistic, it also limits the frequency with which it can viably be conducted for many patients. Thus, we will utilize the Conners CPT as a secondary metric of ADHD symptoms. The Conners CPT is a computerized assessment capable of determining inattentiveness, impulsivity, and capacity for attention in patients [135]. While it is considered less accurate than tests requiring interviews and generally not utilized for diagnosis on its own, utilization will allow for tracking of symptoms at a greater number of timepoints.

The FIBSER scale is a simple test of the tolerability of psychiatric medication and will be utilized for determination of meeting our aim related to the severity of side effects [32].

Study Design & Justification

The clinical trial will examine 5 groups under different conditions to compare the effectiveness of our final design. In Group 1, participants are not diagnosed with ADHD. In Group 2-5, all participants must be diagnosed with ADHD:

1. Currently receiving no ADHD treatment and continues receiving no treatment
2. Currently receiving no ADHD treatment and is given traditional Ritalin LA
3. Currently receiving no stimulant or glipizide treatment and is given our solution
4. Currently taking Ritalin LA and is given our solution
5. Currently taking Ritalin LA and continues taking Ritalin LA

Group 1 acts as a control for participants who are not taking any stimulant to compare with the data of patients who use or will transition to using stimulants. This group will be composed of people not diagnosed with ADHD.

Group 2 and Group 3 allows for comparison between the effect of starting on only Ritalin LA and the effect of starting with our solution.

Group 4 and Group 5 allows for comparison between the effect of transitioning to our solution against a control group that has been using Ritalin LA and continues to use Ritalin LA.

Group 3 and Group 4 can also be compared to obtain data on the effect of using our solution when there was no current stimulant treatment and the effect of transitioning to our solution from an existing Ritalin LA treatment.

Table 1: Description of five patient groups required for Acui-Care's paper testing plan. The set of groups specified will allow for a high level of certainty as to the impact of Acui-Care's solution on both ADHD symptom treatment and appetite suppression as compared to changes resulting from habituation to stimulant medication.

Group	Treatment before trial	Treatment during trial	Rationale
1	No treatment	No treatment	A control to determine variability in endpoints without the influence of methylphenidate or glipizide
2	No treatment	Ritalin LA	A control to determine the impact of stimulant treatment for ADHD without a solution for appetite suppression
3	No treatment	Acui-Care solution	The group receiving our solution as intended, who should see a decrease in ADHD symptoms with limited impact on appetite
4	Ritalin LA	Acui-Care solution	Another primary group of interest, who should continue to see similar levels of treatment for ADHD symptoms and an increase in appetite.
5	Ritalin LA	Ritalin LA	A control group to determine variability in endpoints with only treatment with methylphenidate

To obtain relatively similar groups, stratification by age, gender, and weight will be used to approximately balance groups in advance.

Table 2: Description of stratification for Acui-Care's paper testing plan. Stratification will allow for the creation of physiologically equivalent sample groups to ensure results accurately reflect the impact of the solution across people of multiple ages, weights, and genders.

Category	Stratification
Age	18-24,25-30,31-40,41-50,51-60,60+
Gender	Male-identifying, female-identifying, other
Weight	<100 lbs, 100-140 lbs, 140-180 lbs, 180-220 lbs, 220+ lbs

Study Plan

Our Phase 3 clinical trial will require the observation of at least 3,285 initial participants (see *Statistical Methods* for explanation of calculation) over the course of 2 years. All groups, Groups 1 through 5, will be observed throughout the trial.

Stage 1: Pre-treatment. Patients with ADHD both currently taking Ritalin LA and previously untreated but looking to begin treatment with an extended release stimulant medication will be recruited for this trial, as well as patients without ADHD to act as a control. After being evaluated on our criteria (see *Selection and Discontinuation of Subjects*) they may be included in the trial.

Stage 2: Initial Evaluation. Before beginning with our solution, patients will be weighed and fill out a Food Frequency Questionnaire and Conners Continuous Performance Test. For patients currently taking Ritalin LA, they will also complete the FIBSER Scale. Patients will be asked to provide two patient references, to be used for Conners Scale determinations both at this and the final time point. A psychologist uninvolved with patient treatment will conduct interviews for determination of a patient's score on the Conners Scale.

Patients will then consult with a psychiatrist to determine an optimal starting dosage based on independent guidelines for the glipizide and extended release methylphenidate components. Versions of the Acui-Care solution will be available with doses of methylphenidate from 20 mg up to 60 mg, at 10 mg increments, and of glipizide from 2.5 mg up to 15 mg at 2.5 mg increments. Patients will be provided with information on known medication interactions and possible adverse effects to report.

Stage 3: Dose Titration. For the first month after the initial evaluation, patients will be able to consult with their provided psychiatrist as frequently as necessary (up to once every other day) to modify their dosage of glipizide and extended release methylphenidate to find an optimal combination of doses. Patients receiving Ritalin LA only will be able to complete this same process.

Stage 4: Monitoring. Beginning one month after the initial evaluation and continuing once a month for two years, patients will have their endpoints measured. Patients receiving our solution and Ritalin LA will be weighed, fill out the Food Frequency Questionnaire, and tested with the Conners CPT and FIBSER Scale. Patients receiving no medication will complete the same evaluation except for the FIBSER Scale. After the assessment, patients will meet with a psychiatrist to discuss any concerns they may have and reevaluate their dosing. At the last point, the psychologist will again conduct interviews to determine a Conners' Scale score. Patients will also have access to visits with their psychiatrist at any time during the monitoring phase to address concerns and request changes to their regime.

At any point throughout any stage, the discontinuation or withdrawal of any participant will also be recorded, tracking their reasons for no longer continuing participation in the trial (See *Criteria for Premature Termination of Study* and *Criteria for Discontinuation or Withdrawal of a Subject*).

Criteria for Premature Termination of Study

There are several criteria that would warrant the early cessation of our study. If any new information becomes known about the study drug(s) that indicates an issue with the safety and/or efficacy of our design, then the risk to the study participants will no longer be acceptable. The study may also be halted if there is a significant violation of Good Clinical Practice (GCP), which is an international ethical and scientific quality standard to guide the design and conduct of clinical trials [136]. Additionally, if subjects in more than one group meet one or more of the Group Stopping Criteria, the study may be terminated due to safety concerns.

Group Stopping Criteria. This is a list of potential adverse reactions to one or more of the study drugs in our design. If any subject in any group meets one or more of these criteria then subjects in that group must be given a lower dose for the rest of the study [137]. The Group Stopping Criteria related to methylphenidate (MPH) are hypertension; treatment emergent psychotic or manic symptoms, e.g. hallucinations, delusional thinking, or mania; aggression; seizures; priapism, usually developed after some time on MPH and often occurring after an increase in dose or during withdrawal; peripheral vasculopathy, including Raynaud's Phenomenon; and visual disturbance [138]. The Group Stopping Criteria related to glipizide are severe hypoglycemia and hemolytic anemia [139]. As stated in the introduction to our Paper Testing Plan, MPH and glipizide have no known interactions and thus there are no Group Stopping Criteria for interactions between these drugs.

Selection and Discontinuation of Subjects

In order to determine subject eligibility for this study, we created lists of criteria for inclusion and exclusion of participants, respectively.

Our inclusion criteria is as follows:

- Subject is capable of understanding and complying with protocol requirements.
- Subject is capable and willing to provide written informed consent.
- Subject is aged 18 to 64 years at time of consent. This is the standard age range of the adult population used in clinical trials [140].
- Subject is able to swallow a capsule whole.

Our exclusion criteria is as follows:

- Subject with any of the following: agitation; hypersensitivity to methylphenidate; glaucoma; tics, preexisting psychosis; prior history of seizures, or prior EEG abnormalities in absence of seizures; diabetic ketoacidosis, with or without coma; hypersensitivity to sulfonamide derivatives; Type 1 diabetes mellitus; known renal or hepatic impairment; adrenal or pituitary insufficiency; known glucose 6-phosphate dehydrogenase (G6PD) deficiency; pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia; known structural cardiac abnormalities, cardiomyopathy, coronary artery disease, or other serious cardiac problems; or known gastrointestinal narrowing disorders and strictures in association with the ingestion of drugs in non-deformable controlled-release formulations [138][139].
- Subject is using monoamine oxidase inhibitors. Concurrent use with Ritalin LA may result in hypertensive crises [138].
- Subject is considered a suicide risk, has previously made a suicide attempt, or is currently demonstrating active suicide ideation [6].
- Subject is underweight based on Centers for Disease Control and Prevention BMI-for-age sex-specific values, with underweight being defined as a BMI <3rd percentile [6].
- Subject is significantly overweight based on Centers for disease Control and Prevention BMI-for-age sex-specific values, with significantly overweight being defined as a BMI >97th percentile [6].
- Subjects of childbearing potential or with a partner of childbearing potential who are unwilling or unable to use effective contraception throughout the duration of the study [6][137]
- Subjects who are pregnant or lactating [137].
- Subjects on any sort of weight loss plan or taking any diet medications or supplements, including any appetite stimulants, and who are unwilling or unable to discontinue the plan and/or medications [141].
- Subjects with a diagnosed eating disorder unrelated to any current ADHD medication prescription [141].

Criteria for Discontinuation or Withdrawal of a Subject

There are several reasons a subject may be withdrawn or choose to withdraw from this study. If a subject experiences a pretreatment event (PTE) or adverse event (AE) that poses an unacceptable risk to their health or has made them unwilling to continue, they will be withdrawn. An unacceptable risk would include any of the events listed in Group Stopping Criteria, or other unexpected events of similar severity. If a subject significantly deviates from study protocol, including failing to meet entry criteria and failing to adhere to protocol during the study, or cannot be contacted for follow-up, they will be withdrawn. If a subject becomes pregnant, they will be withdrawn. For any subject withdrawn from the trial by the team, the primary reason for withdrawal will be recorded. Subjects may also voluntarily withdraw from the study for any reason; reasonable attempts to determine and record the reason will be made, but the subjects have no legal obligation to disclose it [137].

For the purposes of this study, we are specifically interested in determining when subjects withdraw due to being unable to find the proper dose for their unique biology. This maps back to our team's design requirement that our product must be personalizable such that the majority of users can find the right dose for them.

Pretreatment Events and Adverse Events

For this study we will record pretreatment events (PTE) and adverse events (AE) experienced by any subject. A PTE is defined as any untoward medical occurrence prior to administration of any study drug and does not necessarily have to be causal with study participation [137]. An AE is defined as any untoward medical occurrence after administration of any study drug and does not necessarily have to be causal with study treatment. These may include any related or unrelated symptom or disease occurring during study participation through the follow-up [137].

Collection. The collection of PTEs begins once the subject signs the informed consent form to participate in the study. The collection will continue until the subject withdraws from the study or is administered the first dose of study drug. AEs will be collected from the time when the subject is administered the first dose of study drug and will continue routinely until 30 days after the last dose of the study drug [137].

Reporting. Subjects may report PTEs at any point up until the first dose of study drug is administered. AEs will be inquired about at routine study assessments for collection, but a subject may also report an AE at any point during the study. Any subject reporting a PTE or AE must be closely monitored until regression of symptoms occurs. For any PTE or AE the following information should be collected: start and stop date and time; frequency; severity; seriousness of event; and outcome. For AEs only the investigator will also record their opinion on the causal relationship between the event and administration of study drug [137].

Medications and Dietary Products Under Observation. In addition to PTEs and AEs, subjects will be asked to report if they use certain medications or dietary products due to potential interactions with our study drug. These interactions primarily have the potential to impact the efficacy of our product, but could also carry a low safety risk. These products are the following: sulfonylurea-class drugs, nutraceuticals, nicotine-containing products, vitamin supplements, alcohol-containing products, poppy seeds, and nonsteroidal anti-inflammatory agents (NSAIDs) [137].

Recording these events allows us to study the safety of our product when taken with or without common comorbid medications. This directly correlates to our safety design requirements of a non-harmful product, and a product that does not have significant adverse interactions with medications for common comorbid conditions.

Statistical Methods

Unless stated otherwise, all tests will utilize $\alpha = 0.05$

As discussed previously in our *Endpoints* section, the quantitative aspects of the clinical trial focus on the participants' answers to the food frequency questionnaire, their physiological changes in weight, and their Conners' Scale, CPT, and FIBSER Scale assessment. Any discontinuation or withdrawal of the subject will also be recorded, tracking the reported reasons for no longer continuing participation in the trial. Furthermore, any medication-related incidents will be logged. This allows Acui-Care to gather data on the efficacy, safety, and tolerability of our solution. Specifically, our solution will be compared to the short-term, critical requirements outlined in the *Endpoints* section via statistical means.

Non-harmful. The number of participants who experience an adverse event will be calculated. No events should be life-threatening, and no more than 0.5% of the participants should experience an adverse event to meet this requirement. We will use a one-tailed test of proportion to determine if the proportion of adverse events is greater than 0.5%

Reduces impact of appetite suppression. The Food Frequency Questionnaire will be used to quantify the impact of appetite suppression. There should be no statistically significant differences in the results from before and after beginning treatment with our solution for groups that are initially not taking medication (Group 3), and there should be a statistically significant increase in food intake for groups that initially are on traditional Ritalin LA that transition to using our solution (Group 4) in order to meet this requirement. Because the FFQ is highly granular, the test will be applied to both the raw data, servings by item, and a "merged" version that will be servings by food group. We will utilize the transformed data as the primary metric.

To test this hypothesis, we will utilize a multivariate, nonparametric test between groups and time points, specifically applying the test described in "A practical affine equivariant multivariate median"(Hettmansperger and Randles, 2002)[142] to the differences between these values. Particular focus will be on the difference between the initial and final time point, though the difference between months will also be studied. Between groups, the corresponding time points will be used, with a focus on the final time point. Here we will utilize the Bonferroni correction to account for the large number of variables being compared.

Table 3: Statistical tests to be applied to appetite-suppression related endpoints. Both controls and a set of primary tests are described. Controls will ensure that the method is capable of capturing the desired effect, while the primary tests will provide information on efficacy in multiple use cases.

Controls			
	Sample 1	Sample 2	Expected Result
App.C.1	Group 1 at stage 1	Group 1 at end of stage 4	No difference in medians
App.C.2	Group 2 at stage 1	Group 2 at end of stage 4	Difference in medians
App.C.3	Groups 1,2,3 at stage 1	Groups 4,5 at stage 1	Difference in medians
App.C.4	Groups 2,5, at end of stage 4	Group 1 at end of stage 4	Difference in medians
Primary Tests			
	Sample 1	Sample 2	Expected Result
App.T.1	Group 3 at stage 1	Group 3 at end of stage 4	No difference in medians
App.T.2	Difference between group 3 at stage 1 and end of stage 4	Difference between group 1 at stage 1 and end of stage 4	No difference in medians
App.T.3	Group 4 at stage 1	Group 4 at end of stage 4	Difference in medians
App.T.4	Group 4 at end of stage 4	Group 5 at end of stage 4	Difference in medians

We will apply the same comparisons as listed for the FFQ, with the primary difference being the utilization of a multivariate parametric method to compare means to the weight data. This will act as a secondary test of appetite -- if no change in appetite is found from the food frequency questionnaire but there is a significant change in weights, we will know there was in fact a difference in diet between time points.

Does not reduce the impact of ADHD treatment. The Conners' Scale and Conners' CPT data will be used to determine the relative impact of ADHD treatment on participants with ADHD. There should be no increase in T- score when transitioning from traditional Ritalin LA to our solution in Group 4. This will be determined using a paired T-test between the first and final time point using the Conners' scale data. Additional controls and tests can be found below in Table Y. For all listed tests within the same group over time, a linear regression analysis for CPT scores will be utilized, where no change in mean would then correspond to no significant difference from a slope of zero and a decrease in mean would result from a negative slope significantly different from zero.

Table 4: Statistical tests applied to endpoints related to efficacy of solution for ADHD treatment. Like the tests for appetite suppression, controls will be utilized to ensure test accuracy and specificity while primary tests aim to demonstrate that the Acui-Care solution is similarly effective to Ritalin LA.

Controls for Conners' Scale Assessment			
	Sample 1	Sample 2	Expected Result
Eff.C.1	Group 2 at stage 1	Group 2 at end of stage 4	Decrease in mean
Eff.C.2	Group 1 at stage 1	Group 1 at end of stage 4	No change in mean
Eff.C.3	Group 5 at stage 1	Group 5 at end of stage 4	No change in mean
Primary Tests for Conners' Scale Assessment			
	Sample 1	Sample 2	Expected Result
Eff.T.1	Group 3 at stage 1	Group 3 at end of stage 4	Decrease in mean
Eff.T.2	Group 4 at stage 1	Group 4 at end of stage 4	No change in mean
Eff.T.3	Group 3 at end of stage 4	Group 4 at end of stage 4	No change in mean
Eff.T.4	Difference between group 4 at stage 1 and end of stage 4	Difference between group 5 at stage 1 and end of stage 4	No change in mean
Controls for Conners' Continuous Performance Test			
	Sample		Expected Result
Eff.C.4	Group 1		Slope not different from 0
Eff.C.5	Group 2		Slope different from 0
Eff.C.6	Group 5		Slope not different from 0
Primary Tests for Conners' Continuous Performance Test			
	Sample		Expected Result
Eff.C.4	Group 1		Slope not different from 0
Eff.C.5	Group 2		Slope different from 0

Does not increase adverse effects experienced by patients. The FIBSER Scale will be used to quantify the participants' experiences of adverse effects. 95% of participants who are initially on traditional Ritalin LA treatment and transition to our solution (Group 4) should not see an increase in experiencing adverse effects to meet this requirement. We will use a one-tailed test of proportion to determine if the proportion of patients seeing an increase in adverse effects is less than 5%. We will compare this to the same rate for group 5 to determine the natural proportion of patients who will begin to find their stimulant medications less tolerable and group 3 to determine tolerability in stimulant-naive patients.

Personalizable; the extended release medication must offer different dosing options. Participants who withdraw and discontinue their involvement with the study can provide reasons for discontinuing the study (see *Criteria for Discontinuation or Withdrawal of a Subject*). No more than 20% of participants using our solution (Groups 3 and 4) must leave the study due to our solution being incapable of providing a dosage suitable for that participant's individual biological and physiological needs to meet this requirement. We will use a one-tailed test of proportion to determine if the proportion of patients leaving on account of being unable to find a correct dose is greater than 20%

Limits adverse interactions with medications commonly prescribed for comorbid conditions. No more than 0.5 percent more of participants taking our solution and taking medication for a comorbid health condition should experience an adverse drug effect above the fraction not taking another medication who experience an adverse event to meet this requirement. We will use a one-tailed test of proportion to determine if the proportion of patients who experience an adverse event in this group is 0.5% higher than the proportion in the group not taking a comorbid medication.

Does not increase frequency of healthcare visits. The participants' frequency of healthcare visits is tracked throughout the duration of the clinical trial. After 2 years, the average rate of healthcare visits should not be greater than once every 30 days to meet this requirement. The average rate does not consider the initial one month period in which the frequency of visits is high in order for dose titration to occur. We will utilize a Wilcoxon signed rank test to determine if the median of the data is significantly different from the 30 days associated. We will accept the case in which the median is higher than the specification.

These statistical methods will help Acui-Care determine whether our solution has met these short-term, critical requirements. Note that not all data, particularly those endpoints collected monthly, are not utilized for these aims. While the overall change during the trial is of primary importance to the Acui-Care team, characterization of patient response over extended use is critical and will inform changes to the design and our plan for administration. This project was inspired by the large drop-off in adherence to stimulant medication regimens over several years, thus it would be irresponsible of us to consider the success of our solution without analyzing trends in our endpoints over the length of the trial. Likewise, beyond completion of the tests described here, data exploration and visualization techniques will be used at the patient and group level to identify effects that were not accounted for in this original plan.

Power Analysis. To determine the necessary size for a group, a power analysis was applied to the primary endpoint, patient weight. In a previous study of the physiological effect of methylphenidate[23], a decrease of 1.07 kilograms was found from before treatment to two months after. We suspect, then, that this difference is the minimum we might measure on account of the impact of appetite suppression. The standard deviation for both time points was approximately 11 kilograms. This results in a d of 0.097. Assuming a false negative rate of β=0.2, corresponding to a power of 0.8, and a false positive rate of α =0.05, we can find n with the formula $n \geq (\frac{z^* + z^*_{1-\beta}}{d})^2$, where z^* and $z^*_{1-\beta}$ are found by applying the qnorm function in R to $1 - \alpha$ and $1 - \beta$, respectively. This yields $n \geq 657$, meaning that for each of the 5 groups, 657 study participants are needed, yielding a study size of at least 3285 participants.

Paper Testing Conclusions

Acui-Care's validation testing protocol was developed to support continued development of our pharmaceutical solution to stimulant-associated appetite suppression in ADHD patients while measuring our progress toward meeting our design specifications.

Our paper testing plan addresses all of our critical, short-term requirements. Based on predicate Phase III clinical trials, it will allow Acui-Care to both validate solution specifications including effectiveness for treatment of ADHD, reduction of appetite suppression and overall tolerability while collecting valuable metadata that can be applied to determination of solution personalizability and burden of usage. Over the course of 2 years, 3285 subjects across five stratified groups will be monitored, with two groups, one never having received a pharmaceutical treatment for ADHD and one having previously taken Ritalin LA, receiving our solution. Pulling from a variety of statistical tests, the trial will utilize a large number of control comparisons to ensure accuracy and precision of measurement while demonstrating solution impact in a number of settings. Monthly measurement of most endpoints will support iteration of the design to meet patient needs and determine recommendations for a dosing regime.

While this testing plan is fairly comprehensive, further steps validation testing include continued study of participants in the proposed clinical trial to determine any possible long-term effects of the solution.

XIII. RECOMMENDATIONS AND FUTURE DIRECTIONS

Design Recommendations

The Acui-Care team feels highly assured by the response of reviewers during their most recent external design review of their overall design inputs, final product, and plan for intended use. However, the solution presented offered only the most simplified mechanism for addressing our critical, short term design goals. Several points made by reviewers matched discussion within the group on additional possible iteration to the design

Risk of Glipizide

A primary concern throughout the design process has been selection of an appetite stimulant with a quick but limited duration of action and limited side effects. Out of the set of options reviewed (see *Design Process: Design Concept #1*), glipizide was selected for its relative efficacy and pharmacokinetic profile. However, glipizide is a sulfonylurea, acting to increase appetite by stimulating insulin release from the beta cells of the pancreas [143]. This mechanism, while effective for increasing appetite and causing weight gain in patients without appetite suppression, has several associated adverse effects, including risk of hypoglycemia acutely and reduced insulin clearance, glucagon levels, and increased sensitivity to insulin over longer periods [143]. Incidence of hypoglycemia serious enough to warrant medical intervention in glipizide users is approximately 2% annually [144], meaning that this component alone may be enough to put our solution outside of the range of likelihood for adverse events in our specifications (see *Design Inputs*). These adverse effects, when considered with other characteristics of the medication, were not considered disqualifying in our original design, but should be remedied in a next generation design. This is representative of the limited quality of appetite stimulants currently available on the market.

During original research into development of an appetite monitoring device (see *Design Process: Design Concept #2*), the Acui-Care team came upon ghrelin, a hormone produced in the human gastrointestinal tract, as a strong candidate as a hunger biomarker. Additional research into ghrelin revealed several studies in which intravenous injection was utilized to increase hunger and reduce wasting [145][146] without direct impact on blood sugar. While it is associated with gastric rumbles and flushing in about 20% of patients when used alone [147], Acui-Care believes the studies conducted thus far point to ghrelin-based therapies being capable of revolutionizing appetite stimulation. Thus, to remedy side effects caused by glipizide usage, we intend to incorporate ghrelin into a future version of the design, though only after a ghrelin-based medication is approved by the FDA for appetite stimulation.

Use in Geriatric Populations

While Acui-Care has marketed our design toward the adult population (i.e. over the age of 21), we were primarily concerned with people on the younger half of this spectrum, generally those of working age. In this, we neglected elderly populations. This was not out of lack of care, rather on account of what we perceived as the limited value of stimulant therapies in this population -- stimulants are used to increase focus for getting through tasks like work or school, but many elderly people are retired. Additionally, stimulants are associated with increased cardiovascular stress, a particular concern for the elderly. However, additional research has shown that methylphenidate may have additional uses in geriatric populations, namely treatment of geriatric depression, apathy, and reduced cognition [148]. The elderly are also at higher risk of low appetite than the population generally [149]. Thus, our solution might be of benefit to them outside of the realm of ADHD treatment.

Extending our solution to this population poses two primary challenges. First, while the cited studies have found efficacy for cognitive treatment, increased cardiovascular strain poses a risk. Second, the elderly are likely to have type 2 diabetes than the population overall [149], meaning that they are more likely to be prescribed a sulfonylurea like glipizide, reducing the fraction of this subpopulation who could use the solution.

To address the first challenge, Acui-Care suggests the addition or coadministration of an extended release beta-blocker to the existing formulation in a next-generation version of the solution marketed to the elderly. Beta-blockers act to reduce heart rate and blood pressure and have been shown to reduce the rate of adverse cardiovascular events in stimulant users [150]. Inclusion would thus increase tolerability of our solution in this population. For managing the higher likelihood of current sulfonylurea usage as well as higher incidence of insulin-related maladies, we again consider alternative appetite stimulants. Ghrelin, as referenced in the previous section, would likely be an ideal choice. However, in the nearer term, dronabinol may be a more viable option for treatment of the elderly [151]. Previous concerns on limited psychotropic effects are less relevant for uses in this population, and concerns on increased rate of central nervous system depression in elderly populations are reduced by coadministration of methylphenidate, a central nervous system stimulant [152].

Non-Design Modifications

In addition to the modifications to be considered in future iterations of the design, Acui-Care recommends further verification testing of drug release, which will be discussed in this section.

Further in vitro and in vivo verification testing

One of the concerns that arose during our second design review was that neglecting the degradation of the enteric polymer coating might give an inaccurate representation of time release. Because of this, Acui-Care has decided to conduct in vitro testing of our glipizide beads to confirm the pH dependent degradation of the Eudragit S-100 coating. We plan to first acquire the materials necessary for making the glipizide beads (See Cost Analysis section) and make the beads using the formulation process our team found in literature. We will then conduct pH dependence testing by placing the beads in a low pH environment and then slowly increasing the pH to model the bead's path down the digestive tract. Our team will collect data on the time necessary to achieve full dissolution of the beads as well as the amount of premature drug release if there is inconsistent breakdown of the polymer coating.

One possible future change that could be made (although Acui-Care is not recommending this for the next iteration of the design) is to potentially mix the Eudragit S-100 polymer with Eudragit L-100 polymer. Eudragit L-100 polymer dissolves at a pH of approximately 5.5, and previous studies suggest that intentionally altering the ratio of the two polymers can alter the dissolution profile of the polymer; furthermore, a combination of the two polymers could overcome the potential gastrointestinal pH variability among individuals [153]. After in vitro tests are conducted, in vivo tests could also be conducted to confirm the time release inside the bodily environment. Should in vivo tests reveal inconsistent time release between test subjects, this additional polymer could be added and in further testing could be conducted both in vitro and in vivo.

Another concern that arose during our second design review was that neglecting the time of drug absorption in the lumen could also give an inaccurate representation of drug release. In vivo testing will allow us to consider absorption time and potentially make changes to the initial drug concentration or the radius of our microbead to accommodate absorption time and successfully induce appetite around lunchtime.

Next Steps

The Acui-Care team believes that they have successfully met their short term, critical design goals, at least within the scope of the course. However, completion of these aims leaves several original goals of the project unmet and would require additional work to meet.

Tolerability and Compliance. Our solution was designed to reduce a specific adverse effect highly associated with decreased tolerability of stimulant medications. We originally reached this aim through research on medication noncompliance, believing that successful completion of the prescribed medication regime would be in patients' best interest. Now having addressed appetite suppression, we direct our focus to tolerability more broadly. Our paper testing plan should be able to determine the impact of reducing appetite suppression on overall tolerability. If tolerability still remains an issue, we would intend to move forward with additional modifications to the underlying extended release stimulant product. Possible avenues include addition of a mood stabilizer based on feedback related to "come-downs" and a delayed release sleep medication, for example melatonin, to ease sleep-related issues. We would continue to compare compliance with our solution to the baseline for stimulant medications as a metric of patient satisfaction.

Expansion of Market. In scoping our solution, we chose to exclude children and adolescents because of a perceived lesser need for direct appetite stimulation within this group on account of having limited autonomy. However, even if children are more likely to be prompted to eat, they still experience associated nausea and may consume less food even if they eat at every meal time. Children with ADHD are prescribed stimulants at a similar rate to adults [154]. However, concerns about the long term side effects of changes to appetite are more relevant on account of their active growth. Solutions for appetite suppression in this group are thus more specific and further research would be required to determine how to meet the needs of this group. Many children also receive powder or liquid products instead of pills on account of difficulty swallowing, so alternative delivery options may also require investigation.

Recommendations for Future Teams

The Acui-Care team is likely done pursuing this design for the time being on account of the members having diverging career aims. That does not imply that the design space has been fully considered in our design. Rather, there is a wide array of possible directions for future engineers to take.

This project began from the perspective of medication non-compliance. The Acui-Care team determined that medication tolerability was the most important factor in patients' decisions to stop their dosing regime. Tolerability is a fairly broad term, and this project only addressed one element of it, appetite suppression, in developing our solution. Outside of that, solutions to a set of fairly critical side effects, including "come-down" irritability and increased moisture loss through sweat and urination were not developed. Development of a solution to any of these problems integrated into an existing extended release stimulant product would increase patient wellbeing, along similar lines to this original project. We recommend further development along one of these other paths.

Acui-Care also recommends utilization of a research tool that was unable to be incorporated into our project due to time constraints: a survey of stimulant users. Joshua, having spoken informally to multiple people prescribed stimulants about issues associated with tolerability, believed that a questionnaire with questions on how individuals mitigate adverse effects of their medication would have been valuable in finding possible solutions that would not be clear from the team's brainstorming and literature review. While stakeholder input was key to the direction of the project, we believe that this "wisdom of crowds" might reveal novel engineering solutions and suggest that such a study be run in advance of future ideation.

Finally, the team suggests that further work ought to be based on a more thorough understanding of neuropharmacology and drug delivery than Acui-Care brought to the process. While the team had background knowledge on the mechanisms of ADHD and stimulant therapeutics, it did not extend to the quantitative level necessary for directly understanding how changes in physiology and medication composition would impact function of the design. The team did not expect that so much of the design would rely on research on mechanisms of hunger or gastrointestinal drug absorption. Becoming knowledgeable enough about these topics to move forward with the design process was a major bottleneck, and the narrowness of our background may have excluded realistic possible designs. For any project related to ADHD relying on administration of additional therapeutics, these skills are necessary prerequisites.

IX. CONCLUSION

After learning about the many negative side effects of ADHD stimulants, our team set out to improve the tolerability of these otherwise effective medications. Specifically we aimed to address the most common side effect, appetite suppression. After scoping down to our target market, adults with ADHD, we outlined our users' needs and design requirements, and then finalized our design outputs. Our design incorporates both an ADHD stimulant and an appetite stimulant, and aims to treat ADHD symptoms while stimulating the patient's appetite at lunchtime. We will deliver the drugs via a microbead technology, which delays the release of half of the ADHD stimulant until afternoon and delays the release of the appetite stimulant until roughly 3 hours after consumption. After completing our design, we modeled the drug release of our microbead core to ensure we could reach peak plasma concentrations by lunchtime while delaying the release. We also planned a Phase III clinical trial to ensure that our design would meet our design requirements and ultimately meet our user's needs. Finally, we planned the future direction of our solution, which includes expanding our market to all ages and including a broader range of commonly prescribed stimulants.

X. APPENDICES

Appendix A. Higuchi Model

Equation

$$f_1 = Q = K_{\mathrm{H}}\sqrt{t}$$

f_1 = fraction of drug released
t = time
K_H = release constant of the drug

For our model we used a K_H of 1.187 hr^{-1}, as this was experimentally determined by a research group for 5 mg of uncoated glipizide in tablet form [80].

Matlab Code

```
x = [0: .01: .71];  %limits the y values from 0 to 1
y = 1.187*x.^(.5);

plot(x,y);
xlabel('Time (hrs)')
ylabel('Fraction of Drug Released')
```

Appendix B. Calculating Quantities of Our Materials Needed

Calculating Number of Microbeads

Volume of microsphere: 4/3*π*90 um^3 = 3053628 um^3
With a glipizide concentration of 2.55E-10 mg/um^3, the amount of glipizide in one bead is:
2.55E-10 mg/um^3* 3053628 um^3 = 7.787E-4 mg

5 mg / 7.787E-4 mg ≈ 6422 microbeads

Calculating Volume of Glipizide in Each Bead

Density of Glipizide: 1.3E-9 mg/um^3
7.787E-4 mg/1.3E-9 mg/um^3 = 598,981 um^3

Calculating Weights of Coagulants

Density of HPMC: 1.3E-9 mg/um^3
Density of LMP: 1.3E-9 mg/um^3
LMP:HPMC ratio: 7:3

Density of remaining space in core:
(1.81E-9*7 + 1.39E-9*3)/10 = 1.684E-9 mg/um^3

Volume remaining in each microsphere:

3,053,628 um^3 - 598,981 um^3 = 2,454,647 um^3
Weight of remaining space in core:
1.684E-9 mg/um^3*2,454,647 um^3 = 0.004134 mg

A 7:3 ratio yields:
0.00289 mg LMP per bead
0.00124 mg HPMC per bead

0.00289 mg LMP*6422 beads = 18.56 mg per capsule
0.00124 mg HPMC*6422 beads = 7.96 mg per capsule

Calculating Weight of Eudragit

Volume of Eudragit Shell Needed:
Shell Thickness: 43 um
Outer Sphere: 4/3*π*133 um^3 = 9854702 um^3
Inner Sphere: 4/3*π*90 um^3 = 3053628 um^3
Volume Eudragit-S per bead: 9854702 um^3 - 3053628 um^3 = 6801075 um^3 per bead
6801075 um^3*6422 = 4.368E10 um^3 per capsule

Density of Eudragit: 1.02E-12 g/um^3

1.02E-12 g/um^3*4.368E10 um^3 per capsule = 0.045 g per capsule

Appendix C. Modeling with Matlab

Matlab Code

```
%Parameter Setup
x = [0:.1:1.6]; %sets range of x-axis
R = 90; % radius in micrometers
K = 1.74859E-8; %erosion rate constant
C0 = 2.55E-10; %mg/(micron^3)

%Hopfenberg equation
y = (1-(1-((K.*x)/(C0.*R))).^3);

%plotting
plot(x,y);
yline([1],'--')
xline([1],'--')
xlabel('Time (hrs)')
ylabel('Fraction of Drug Released')
set(gcf,'color','w');
set(gca,'fontname','times')
```

Calculation of k_{ero}

Important Values:
Microbead radius — 480.44 μm
Microbead drug content — 15.74%
LMP density — 1.81 x 10-^{9} mg/μm3
HPMC density — 1.39 x 10^{-9} mg/ μm3
Glipizide density — 1.3 x 10^{-9} mg/ μm3
LMP:HPMC ratio — 7:3
Time for full microbead release — 7 hours

Calculating Density of Microbead:

$$\frac{\left(\left(\frac{(1.81 * 10^{-9} * 7) + (1.39 * 10^{-9} * 3)}{10}\right) * 85\right) + (1.3 * 10^{-9} * 15)}{100} = 1.624 * 10^{-9}\ mg/\mu m^3$$

Calculating Mass of Microbead:

$$\left(\frac{4}{3} * \pi * (480.44)^3\right) * 1.624 * 10^{-9} = 0.754\ mg$$

Calculating Number of Microbeads:

$$\frac{100}{0.754} = 133\ microbeads$$

Calculating Drug Content of Microbead:

$$\frac{15.74}{133} = 0.118\ mg$$

Calculating Initial Drug Concentration:

$$\frac{0.118}{\frac{4}{3} * \pi * (480.44)^3} = 2.55 * 10^{-10} mg/\mu m^3$$

Rearranging Hopfenberg:

$$k_{ero} = C_0 * \frac{R}{t}$$

Final Calculation of K_{ero}:

$$2.55 * 10^{-10} * \frac{480.44}{7} = 1.749 * 10^{-8}\ \frac{mg}{\mu m^3 * hr}$$

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