A Universal Eye Drop Adherence Monitor to Measure and Improve Adherence to Ocular Medications

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Significance

Glaucoma is a chronic eye disease associated with visual field loss and optic disc cupping.[10] It is the second leading cause of visual impairment worldwide,[1] and will affect up to 80 million people by 2020.[11] The number of people with glaucoma is expected to increase by 50% in the next 10 years as the population becomes increasingly older.[12] Visual impairment is a devastating public health and medical issue for patients, their families, and their communities with a cost to the US government of $6.2 billion in 2011.[13-16]

Glaucoma eyedrop medications are the most common method of treating glaucoma.[2] About 15 million individuals take glaucoma eye drops worldwide. Studies show that these drops reduce the development or worsening of glaucoma by at least 60%.[3-5] Glaucoma eye drops must be taken every day to be effective. However, adherence with prescribed glaucoma treatments is poor,[6-8] and is arguably the largest barrier to preventing vision loss from glaucoma.[17,18]

Poor adherence to glaucoma eye drop medications, defined as using less than 75% of expected doses, occurs in approximately 50% of glaucoma patients.[19-22] Poor adherence results in vision field progression, greater visual loss, and higher risk of blindness.[23-25] At least 3 million individuals worldwide lose vision from glaucoma each year due to poor adherence with eye drops.[23-25] Researchers have difficulty determining the reasons for poor adherence because they have inaccurate methods of measuring adherence with eye drops, which creates large gaps in knowledge.[8] Patients routinely overstate their level of adherence using self-reporting[8], and pharmacy records may be incomplete, inaccurate, and difficult to obtain for individual patients.[26] Researchers have used the MEMS cap, which is designed to measure pill counts,[27] to measure adherence with glaucoma medications.[25,28,29] However, this “bottle within a bottle” mechanism for eye drop compliance requires that the patient remove the MEMS cap, remove the eye drop bottle, remove the eye drop bottle’s cap, dispense the eye drop, replace the bottle’s cap, replace the bottle in the MEMS cap container, and replace the MEMS cap. This 7-step, cumbersome process obviously deviates from the usual process of administering eye drops, thereby limiting the applicability of the device. Overall, a suitable eye drop monitor is not available.[9]

A universal eye drop cap monitor, a device to accurately measure and improve eye drop-taking behavior with all eye drop medications, is a critical need for clinicians, researchers, and patients.[9] We hypothesize that improving medication adherence to eye drops would prevent millions of individuals from losing vision due to glaucoma and other ocular diseases that require chronic eye drop treatment (e.g. uveitis, cornea transplant, dry eyes). An eye drop monitor may also provide tremendous commercial value (see global adherence market below). A universal eye drop cap monitor would help patients to improve eye drop adherence; allow researchers to measure adherence; determine the factors related to glaucoma adherence; and develop targeted interventions to increase adherence in the future.

The **Devers Drop Device (D3)** is a first-generation prototype that we developed to measure eye drop adherence. We propose that this patent-pending drop monitor will accurately measure eye drop adherence with all FDA-approved eye drop bottles. The D3 housing includes a silicone sleeve that securely attaches to any eye drop bottle cap while still permitting normal rotation of the bottle cap and ensuring an FDA-compliant, watertight closure (Figure 1). The monitoring component consists of a robust, magnetic proximity sensor capable of detecting when the eye drop bottle cap has been removed and replaced from the bottle. The device accurately tracks when eye drops are administered by recording the time of cap removal and replacement and communicates adherence data through a secure wireless connection. When an eye drop bottle is empty, the device can be removed from the bottle cap and transferred to a different bottle.

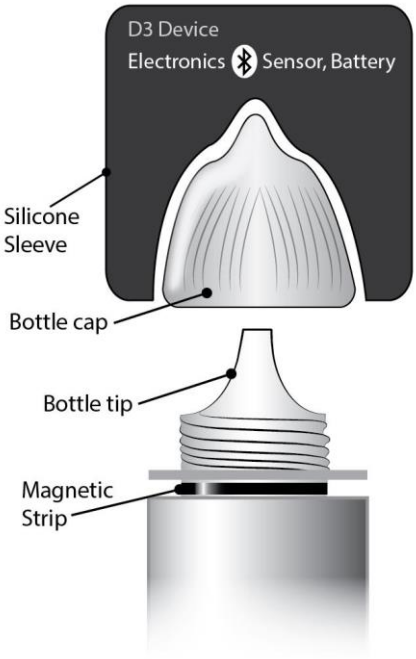


Figure 1. D3 Model

The **global adherence market** has tremendous financial potential. Poor adherence is associated with worse healthcare outcomes, including lost vision, which has significant costs to society.[16] The pharmaceutical industry likewise loses billions of dollars each year due to infrequently-filled or unfilled prescriptions. These losses have inspired several companies to create smart devices (e.g. GlowCap® (Vitality, Inc. Los Angeles, CA), AdhereTech Smart Wireless Pill Bottle (New York, NY), and SMRxT Smart Bottle (New York, NY)) to connect to the Internet and measure adherence with oral tablet medications. Patients, insurance companies, and pharmaceutical companies are increasingly using these devices to improve oral pill adherence. The global medication adherence market is expected to grow at a 17.5% compound annual growth rate (CAGR) worldwide through 2022. We expect a similar growth rate for an eye drop monitor because of the increasing prevalence of glaucoma and other chronic eye disease. But similar adherence devices are not available for eye drops because of unique regulatory and technical challenges (see below under Innovation section).

Overall, this proposal has **high significant impact** to patients, researchers, eye care providers, the public health, the global adherence market, pharmaceutical companies, and translational health behavior research. Currently, researchers have inaccurate and unreliable methods of measuring adherence with eye drops, which creates large gaps in knowledge. Successful completion of the proposal will create a new tool that will transform the research of glaucoma adherence. The collected data will also provide preliminary information about how different electronic reminders can improve eye drop adherence. A future STTR Phase II proposal on a consumer-ready version of the D3 will allow research into self-care for patients and their families to improve eye drop adherence. Improving medication adherence for eye drops would prevent millions of individuals from losing vision due to glaucoma and other ocular diseases that require chronic eye drop treatment.

Innovation

Eye drops present unique challenges for measuring adherence compared to devices that measure oral pill usage, as pharmacies can dispense pills in generic containers. In contrast, the FDA approves an eye drop medication only after its eye drop delivery bottle shows suitable sterility, drop quantity, and drop volume. An

adherence or dose monitor for eye drops must utilize the FDA-approved bottle for that medication, without modification, and without interfering with drop delivery. Further, unlike oral pill bottles, eye drop bottles cannot be reused.

Universal Adherence has received a favorable response to their patent filing (PCT/US16/15600, January 29, 2016) for their innovative prototype that fits more than 25 different types of ocular hypotensive medications that use 10 different bottle caps. The monitor design allows re-use on subsequent bottles for the life of the monitor, which provides value and minimizes additional cost over the life of the device. Our proposal includes several innovative aspects: 1) Utilizes a unique, collaborative group of electrical, software, and mechanical engineers combined with accomplished clinician-scientists to solve complex human, engineering, and behavior problems related to development of an eye drop monitor. 2) Designed for universal fit, the device adapts to the shape of the dropper bottle cap for robust use with all FDA-approved eye drop bottles and does not interfere with routine eye drop delivery. 3) The use of integrated, low-power electronic sensors enables recording of bottle usage information without contacting the sterile contents. 4) Automated, wireless data upload enables real-time adherence monitoring and supports remote intervention for increased adherence. 5) Develops a commercial eye drop cap monitoring device that can automatically track bottle usage, and alert the patient if a dose has been missed. 6) Shifts glaucoma adherence research from indirect methods of determining adherence (pharmacy records, patient report) to direct methods of measuring eye drop taking behavior. This will provide new avenues for glaucoma compliance research. 7) Includes the first study to use a randomized clinical trial to simultaneously evaluate several electronic reminders and will provide preliminary data for a future clinical trial to determine the effect of different interventions for improving glaucoma compliance.

Previous dose monitors are listed as FDA Class I devices and we will register the D3 similarly. The Travatan Dosing Aid uses a mechanical level to dispense and record an eye drop for only one brand (travoprost). It is subject to inadvertent dosing, inaccurate results, wired connection[20] and is no longer available. Other eye drop adherence devices, like the Eye Drop Administration Monitor[30], Ophthalmic Dose Compliance Monitor[31] and the Microprocessor Controlled Compliance Monitor[32] are not available because of the devices' poor scalability, difficulty of use, and awkward bottle attachments. Electronic adherence devices designed for oral tablet medications (e.g. AdhereTech Smart Wireless Pill Bottle, SMRxT Smart Bottle, and GlowCap) cannot accommodate eye drop medications or adapt universally to dropper bottles. Overall, the development of an eye drop monitor will provide significant innovation to research, consumers, and the pharmaceutical industry. We hypothesize that opening and closing the bottle will accurately reflect usage, which is supported by data from oral tablet monitors[39].

Approach

Over the last 5 years, Universal Adherence and Oregon State University have developed a strong collaborative relationship. Aided by two small pilot research grants, we developed the patent-pending "Devers Drop Device (D3)" monitor prototype to accurately measure eye drop adherence. We evaluated several design options with different materials, electronic functions, power requirements, methods of creating a universal fit, and adherence data management. Figure 2 depicts earlier alternative designs including clamp and gear based mechanisms (left side), alternative bottle-site attachments with wired connection (center picture), and the current prototype (right side). We designed, built, and tested the proof of concept eye drop monitors with the following aspects: 1) universal fit for eye drop bottle caps, 2) accurate measurement of eye drop bottle cap removal, and 3) reliable data collection and transmission. The current prototype was successfully tested using ten different eye drop bottle cap types. The device securely attached while maintaining a water-tight bottle closure, allowed normal rotation, and permitted easy removal of the eye drop bottle caps. The silicone sleeve allows easier cap rotation and removal especially for patients with difficulty squeezing the bottle.

Figure 2. Previous D3 Prototypes

The D3 prototype includes a proximity sensor capable of detecting when the eye drop bottle cap has been removed and replaced, and the device accurately stores these dates and times. It wirelessly transmits this data within a range of 1 meter. While mechanically and electrically functional, it requires additional work to adapt the existing prototype for use in the field. In particular, the mechanical design must be adapted from a hand-built design to a robust, scalable manufacturing design, including the use of durable silicone materials for long-term use in the home setting. The prototype size is much larger than desired because of general-purpose electronics modules, requiring 2-3 cubic inches of interior volume. These modules limit battery life to a few days of continuous operation. The proposal below will develop a commercially-viable eye drop monitor.

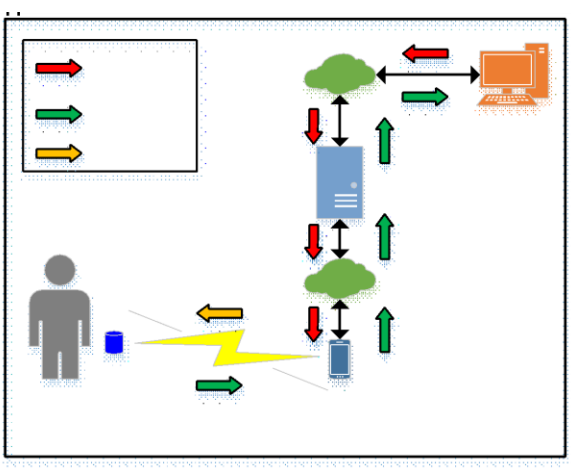
Specific Aim 1: Design a universal, compact, wireless eye drop adherence monitor that can be fit onto any existing FDA-approved eye drop bottle cap.

The prototype D3 module (Figure 2) served a functional demonstration of the core eyedropper adherence monitor, built using general-purpose manufacturing methods and off-the-shelf electronics. To support a clinical evaluation of the efficacy of the D3 (Aim 2), Oregon State University will lead the development and produce a robust, deployable, updated, user-ready version of the D3. This unit must survive long-term use in the clinical study, and it must be reliable, easy to use, and designed with parts that can be produced at low cost with higher volumes in the future. In this Aim, we propose to leverage the initial D3 prototype to: 1) improve design of the custom electronics module in order to shrink the total sensor and transmitter volume to <0.2 cubic inches, allowing a mechanical enclosure sized comparably to a dropper bottle cap, 2) create a continuously operational device utilizing a coin cell or rechargeable battery that provides daily wireless data upload of >4weeks, 3) use durable silicone materials to enable robust, daily operation for >12 months, 4) develop a software interface and infrastructure for wireless, smart phone automated collection of adherence data. Each of these proposed improvements is described here in more detail.

Low-power wireless electronics module. Oregon State University will design a complete electronics module on a small (<0.2 cubic inch), flexible printed circuit board (PCB) to easily integrate into the device housing, and will include an accelerometer as well as a magnetic proximity sensor to support multiple cap removal mechanisms. The use of a static sensor will enable robust monitoring if the bottle is carried in a bag or on the person, and an accelerometer enables exploration of positional or rotational detection for future improved methods of detecting eye drop administration. We will integrate a single-chip Bluetooth Low Energy (BLE) transceiver (Nordic Semi) to support low-power transmission of adherence data to a smartphone. The BLE chip also includes an on-board microcontroller, which will control detection, time stamping, and transmission of each cap removal.

A standard coin cell battery (CR2032) will power the complete custom PCB and is expected to provide 8 weeks of continuous operation without replacement. We will conduct testing in the lab to confirm continuous operation including once-a-day wireless data upload. For a future commercial version of the D3, we anticipate a small, rechargeable battery cell; for the observation study, a single-use battery is chosen to simplify operation. By leveraging low-cost PCB manufacturing and large-volume sensor and processor chips, we anticipate an assembled electronics module cost of <$30, which can scale to <$10 in commercial volume manufacturing. The Bluetooth wireless interface will allow companion software for a variety of smartphone interfaces.

Mechanical Design. A key identifier of the proposed eye drop adherence monitor is that it will provide a universal fit platform for all eye drop dispensers currently available in the market place. This requires a form factor capable of adapting to different eye drop bottles. We prefer a modular design that separates the electronic and mechanical components. This design will allow easier modification if a new eye drop medication bottle cap is released, and the higher cost embedded in the electronics module needs to be incurred only once. Compared to the D3 prototype, the design will be adapted to incorporate more durable silicone materials and plastics, a smaller overall form factor enabled by miniaturized electronics, and a scalable, manufacture design. Additive manufacturing, utilizing PLA/ABS materials, will be used to realize the mechanical attachment module and electronics casing; while the mechanical gripper and any moving parts will be fabricated in metal to guarantee reliability and durability. In the pre-production manufacturability stage, we will not explore manufacturability of a high-volume commercial product in detail. However, the low-volume manufacturing strategies employed here will lay the foundations for a commercial product, while emphasizing the ease of manufacturing for affordable pre-production product testing.



Mobile Application/Software Interface. Oregon State University will develop a D3 software application for an Apple iOs smartphone. The D3 monitor will collect and store time-stamped adherence data after each cap removal event. After each event and again at noon and midnight, data will automatically be transferred wirelessly from the D3 to a mobile device. The mobile application will send reminders via push notifications to the mobile phone and audio and visual alerts to the D3 device. The app can be programmed to give alerts at any time, and will not give an alert if the cap was previously removed within a specified time of the desired dosing. The mobile application will allow researchers to communicate with the D3 device to view up-to-date adherence data and to remotely alter programmed alerts. In the future STTR II grant, the D3 app will focus on patient self-care by providing, immediate HIPAA-compliant adherence feedback through a simple interface to the patient and selected contacts - like family members and physicians.

Prototype Testing. The prototype testing of the D3 will be completed in a controlled laboratory environment. As an iterative process, Universal Adherence will test new prototypes, suggest alterations to the design and function, and re-test until the device meets the customer requirements from the perspective of durability, and functionality. Universal Adherence will verify the silicone sleeve effectively attached, rotates, and detaches from 10 different bottle cap types. Universal Adherence will test durability using International Safe Transit Association 1A drop testing, and long-term wear and tear. We will test functionality by verifying that each device accurately collects adherence data, sends push notifications, visual and audio alerts, and connects using blue tooth to the mobile app. We will also determine sensitivity to errant physical stimulation like shaking, indentation, or jostling in a purse or pants pocket. Battery testing will be performed at Oregon State University with special focus on battery life with and without notifications.

***Potential Problems and Alternative strategies*.** This proposal includes previously successful prototypes and a unique, diverse team of engineers and clinician-scientists to complete the combined engineering and clinical problems of Aim 1. However, it is possible that we may need to test several prototypes in form factor, software, and performance. It is possible that this may require several months to resolve but the 8 months of development time (see below) should be enough time to complete working prototypes (for Specific Aim 2).

Specific Aim 2: Conduct a randomized, prospective clinical trial to determine the ability of the next-generation D3 eye drop monitor to measure and improve glaucoma adherence.

We have not tested any of the previous prototypes in the clinical environment with actual glaucoma patients in common clinical situations, nor determined patient/customer requirements from the perspective of functional, physical, and sensory performance. Universal Adherence will perform the clinical trial using glaucoma patients from the Legacy Devers Schnitzer Glaucoma Center in Portland, OR.

Randomized, prospective clinical trial: We will enroll 50 participants (25 male, 25 female) into a prospective trial with a duration of up to 50 days. The inclusion criteria are those who are prescribed latanoprost eye drop to be used once per day at bedtime, and own a functioning Android smartphone or Apple iPhone iOs) with Bluetooth and cellular connectivity. We will exclude subjects who currently use smartphone medication reminders and those with severe cognitive impairment limiting their ability to understand a questionnaire. The 50-day period is useful for glaucoma studies because subjects revert to their normal dosing pattern within two weeks after their last visit.[33] Also, the 50-day time period allows us to test battery life and storage of electronic data during a typical research period. This study will include two stages: Stage 1) a 25-day period (±3 days) evaluating baseline patient adherence with the D3 device; and Stage 2) a subsequent 25-day (±3 days) period to determine the effect of the D3 device with no reminder versus a daily alert from the D3 device and smartphone.

Stage 1 (Enrollment): At the enrollment visit, the project coordinator will 1) set up a subject account and link the account to the D3 device, and then help the subject download an ESP Touch app to the subject's phone. We will give them written instructions on how to connect this device to their home WIFI, and we will provide a phone

number to call for help with any WIFI connection challenges; 2) provide 2 sample bottles (1 bottle at beginning of Stage 1, and then if subject qualifies for Stage 2, they will receive a 2nd bottle at that time) of latanoprost for the duration of the study and show how to mount the D3 device onto the bottle cap; 3) train the subject to administer the eye drop using the device under clinical guidelines[34] for administration of eye drops; 4) administer a pre-study questionnaire and the glaucoma treatment compliance assessment tool (GTCAT); and 5) instruct subjects to use their latanoprost eye drop nightly per their usual routine, and provide a diary to record difficulties, suggestions, and any other inputs they may have during the study. They will be asked to record any time they forget or are unsure if they took their eye drops. The participants will also initial the diary once a month to ensure they are using it. The D3 device will remain attached to the latanoprost eye drop bottle cap and track when the bottle cap is removed as a measure of medication adherence. After 2 consecutive business days (M-F) of no device communication, the project coordinator will contact the patient by phone to check on the device. This maximizes safety and decreases loss of data from device malfunction. We will record this intervention when it occurs. After 25 days, the project coordinator will compute a compliance percentage using the dosing monitor by dividing the number of days the dose monitor recorded dosing within 3 hours of the prescribed time by the number of days in the study cycle.The first day will be excluded from calculations to allow time to connect to WIFI. Thus, a participant who misses 3 days out of 25 days will be considered (22/25) 88% adherent and this will be their baseline adherence.

Stage 2 (Randomization): after 22 days up to 28 days. If the subject's scheduled day lands on the weekend: We will only include those subjects with <90% baseline adherence in Stage 2 to determine the effect of reminders. Those subjects with >90% adherence will exit the study, and their device and diary will be returned to the study coordinator. We use the 90% cut-off to avoid lack of variability from enrollment bias (e.g. improvement in behavior from enrolling in a study), which will allow us to detect an improvement in adherence and is similar to a previous study design.[35] The project coordinator will use a random number generator to randomize the subject to either Group 1 with the device and no reminder, which is the most common clinical situation, or Group 2, which will have the device with reminders. For Group 1, there will be no changes to their instructions or smart phone. For Group 2, subjects will receive alerts starting at the scheduled dosing time, and the alerts will continue every 10 minutes until the bottle cap is removed. Group 2 will receive no reminder if the eye drop bottle cap is removed within 3 hours before their scheduled time of dosing. The first day will again be excluded from calculations.

Subjects will be given a refill if they run out of the medication prematurely. The bottles will include a previously applied, child-safe magnetic strip on the bottleneck. Magnetic sensing is common in proximity sensors because magnetics provide robust accuracy; are commonly available; use inexpensive technology; are medically safe; and require low battery power.

(Exit) 22-28 days after Stage 2 visit: Subjects will return the device and subject diary to the coordinator and then will complete the survey and GTCAT.

Compensation: All subjects will receive a one time payment of $50.00, which will be loaded on to a MasterCard at the completion of the study. (This could happen at the end of Stage 1 if they do not qualify for Stage 2).

Analysis: Sample Size: Previous studies from our group showed that participants administered 78% of drops with a left-skewed distribution and approximately 85% with less than 90% adherence (cut-off for enrollment in Stage 2). With an alpha of 0.05, and an effect size of 10%, we require a sample size of 36 persons for a power (beta) of 0.80 in each group. Because of time and cost constraints of an STTR Phase I grant, we expect to recruit approximately 42 subjects (85% of 50 participants with <90% adherence for Stage 2 study) with 21 participants per group. While this sample size will not be enough to determine whether one method of reminders is statistically different, it will provide preliminary data for a future, larger, randomized clinical trial.

Pre-study Questionnaire: We will administer a pre-study questionnaire to collect participants' socio demographic information at the first study visit.

Glaucoma Treatment Compliance Assessment Tool (GTCAT): We will administer the GTCAT, a Likert-type questionnaire regarding adherence to glaucoma treatment, at the first and last visit. The GTCAT will provide information regarding participants' self-reported adherence and will reflect changes in self-reported adherence caused by the introduction of the D3 device.

Qualitative Survey: We will also measure the participants' satisfaction with the dose monitor using a short Likert questionnaire. This questionnaire includes questions regarding ease of use; whether they would use the device again; how the device is different from using the medication alone; how much they would pay out of pocket for the device; and other open-ended questions. This will provide satisfaction and preliminary information about the direct to consumer market of the device. This information will supplement information from the participant diary.

Potential Problems and Alternative strategies: We may be unable to complete or have missing data for Aim 2 if we have low recruitment, large drop out of participants, loss of the devices, or malfunctioning of the devices. Devers Eye Institute represents over 20,000 glaucoma patient visits per year and provides a fertile ground for recruiting participants from diverse ethnicities. We will extensively test devices prior to the observational study and will provide on-site and/or at-home replacement and repair of malfunctioning devices, which we expect to be a rare event. We may also enroll participants with high adherence, which may decrease the sample size for Stage 2. However, this pilot study will provide preliminary information for a future, larger clinical trial.

Timeline and Project Milestones

Task	Personnel	M1	M2	M3	M4	M5	M6	M7	M8-12
Pre-Design: Features; Battery and processor module selection; Final requirements definition	All investigators								
Form Factor Re-Design: Miniaturize; new electronics modules; incorporate alarms	Porter, MS Student								
Patient Satisfaction of Re-Design: testing of new form factor.	Mansberger, Kinast, Proj Coord								
PCB Design: Custom printed circuit board (PCB) schematic design and layout; PCB fabrication, assembly, and electrical test	Johnston, MS Student								
Firmware Design: Firmware development, Bluetooth communication, sleep/wake, and event recording; Port to custom PCB hardware	Johnston, MS Student								
Mobile App Design to transfer and access adherence data via Bluetooth smart phone	Porter, MS Student								
Prototype Testing and Adjustments of new Firmware and Software	All investigators								
Clinical Trial: 50 patient on-field testing of device accuracy	Mansberger, Kinast, Proj Coord								
Patient Satisfaction: Surveys of patient satisfaction of device on 50 patients	Mansberger, Kinast, Proj Coord								

Future Directions: At the end of Phase I funding, we will have a research-version D3 prototype that has been tested for use in glaucoma patients. In a Phase II application, we will pursue additional refinements based on the results of the Phase I along with small scale manufacturing to serve the research market, and we will develop a consumer-ready version of the D3. We anticipate software and industrial design improvements will permit a seamless and simple customer experience with real time adherence feedback for patients and their contacts. This will provide a new market to patients, employers, and pharmaceutical companies.

Research Sales**:** We estimate there are about 200 eye drop adherence research teams worldwide and at least 50% of the teams would purchase roughly 100 D3 devices every 3 years based on our prior experience with the MEMS cap. We expect this high market penetration because no quality alternative to our device exists. The research version of the device would sell for $150/bottle, and an accompanying customized research software package would cost $1500. The research version of the device could therefore generate $500,000 in yearly revenues. These limited revenues would help us establish satisfactory device parameters and lead to product refinement for an FDA-approved consumer device and make Universal Adherence attractive for partnerships and equity investments. The research device would also generate new grants and research in eye drop adherence that would result in preserved vision for millions of individuals. Direct-to-Consumer Patient Sales: Approximately 3.5 million glaucoma patients use eye drop medications in the United States and 15 million worldwide. Glaucoma patients take on average 1.8 eye drop medications.[36-38] If 1 in 20 glaucoma patients used our eye drop monitor on 1.8 eye drop bottles, at a price of $30/device our yearly glaucoma patient sales would be $10 million in the US and $40 million globally. This estimate does not include device sales from post-surgical patients or those with eye infections, dryness, or other ocular diseases. It will also create new research avenues in social cognitive theory, and patient activation.

Self-insured employers, pharmaceutical companies, and adherence companies**:** Adherence companies (e.g. Vitality, AdhereTech) have chosen to focus on self-insured employers and pharmaceutical companies as their primary revenue source. Instead of selling directly to the consumer, they are forming wellness agreements with large companies, like banks, and then uses their devices to improve patient adherence, improve patient health, decrease employee health costs, and increase pharmaceutical revenues. Universal Adherence will also explore licensing our intellectual property to employers and pharmaceutical companies, as well as to other adherence companies to enlarge their adherence device portfolio to include eye disease.