AMERICAN ACADEMY OF OPHTHALMOLOGY®

Is CONNECTDROP®, a Medication Event Monitoring System Add-On Paired with a Smartphone Application, Acceptable to Patients with Glaucoma for Taking Their Daily Medication? The CONDORE Pilot Study

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Objective: This pilot study tested the feasibility of a future efficacy trial examining the effect of CONNECTDROP®, a novel Medication Event Monitoring System (MEMS) paired with a mHealth application, on medication adherence in patients with glaucoma.

Design: A single-center, single-arm, prospective interventional pilot study (NCT04552964).

Participants: Adults with glaucoma managed with at least a fixed combination of timolol/dorzolamide who are adherent to treatment.

Methods: Participants (n = 31) were provided with the MEMS device and a smartphone with the application installed. They were required to use the MEMS with their usual timolol/dorzolamide prescription for 9 weeks. The study endpoint was at the end of week 9, when all study materials were returned, and participants completed a 17-item patient satisfaction questionnaire. Data collected continuously by each MEMS for the 9 weeks were analyzed for their suitability to quantify adherence of the individual participant and characterize adherence trends within the study cohort. Clinical data were collected at baseline, week 8, and week 9 for the safety evaluation.

Main Outcome Measures: The primary outcome was global patient satisfaction after 9 weeks. Secondary outcome measures included participant feedback on handling the MEMS and its usability, along with that of the connected application. Objective data were used to determine participant medication adherence. The proportion of participants who successfully changed the MEMS to a new bottle at week 8 was reported.

Results: The MEMS-connected device achieved a global satisfaction score of 74.1% from study participants after 9 weeks. Furthermore, 70.4% of participants found the MEMS easy to use. However, only 59.2% reported feedback from the mHealth application useful in reminding them to take their treatment. MEMS-derived data showed that 70.4% of participants achieved an "adherence score" of 80% or above after 8 weeks and that 40.7% who completed the study had not changed the bottle correctly. No adverse events (AEs) were reported.

Conclusion: In this pilot study, the CONNECTDROP device was able to monitor daily intake of anti-glaucomatous medication over 2 months and had high satisfaction amongst this cohort of patients and was easy to use. The objective adherence data obtained appears reliable but must be validated for use in an efficacy trial.

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Poor treatment adherence is prevalent among patients with glaucoma and has been linked to increased disease-associated morbidity.[1–4] The estimated rate of nonadherence to topical medication in this group of patients is estimated to be between 16% and 30%.[5,6] The risk factors described for nonadherence in patients with glaucoma include younger age, African descent, shorter medication time, lower educational attainment, and decreased scores on mental status and depression scales.[6] Commonly reported barriers to medication adherence in patients with glaucoma include poor self-efficacy, forgetfulness, fear of side effects, and difficulties instilling the drops or keeping to the medication schedule.[7,8] Patients with lower treatment adherence have accelerated visual field deterioration.[3,4,9] Sleath and colleagues have shown that patients with glaucoma who are less than 80% adherent to their medication were significantly more likely to have worse vision defect severity.[4] The subsequent preventable vision loss is linked

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to significant health-related costs to patients and clinical burden to health care providers.[10,11]

There is currently no "gold standard" for measuring adherence.[12] To determine medication adherence in their glaucoma patients, physicians rely on objective clinical evaluation such as intraocular pressure (IOP), prescription refill data, or patient subjective self-reporting, which is demonstrably unreliable.[5] Furthermore, there is a body of evidence that suggests that physicians are poor at predicting adherence in their patients.[5,13]

Electronic measurement of patient adherence, Medication Event Monitoring Systems (MEMS) have been evaluated in patients with glaucoma over the last 3 decades.[5] Their use to date has been limited to the experimental setting, where these devices have been instrumental in demonstrating the extent of treatment nonadherence in patients with glaucoma.[5] Medication Event Monitoring Systems devices such as the MEMs 6 Smartcap (Aardex Group)[14] and the Travatan dosing aid[15] are early examples evaluated in glaucoma patients. Recent evaluated technologies include an eye dropper sensor system using waveform analysis associated with deep learning.[16]

Smartphone use has become ubiquitous worldwide, with a predicted 4.68 billion mobile phone users globally in 2019.[17] As a result, smartphone applications developed to improve patient health have proliferated. Termed "mHealth"—or mobile health—it is loosely defined as “medical and public health practice supported by mobile devices”.[18] These applications have the potential to revolutionize how patients and healthcare providers (HCPs) access healthcare, although substantial evidence that mHealth interventions directly improve patient outcomes is currently lacking.[19] Nevertheless, recent metanalyses provide evidence for the efficacy of mHealth to improve treatment adherence in a diverse range of chronic diseases such as hypertension[20] and diabetes mellitus.[21] Moreover, several systems where a MEMS device is connected to an mHealth application to improve adherence in patients with glaucoma are in development. Examples such as Kali Drop (Kali Care),[22,23] which transmits device data wirelessly and is accessible through a user-friendly interface, and an "intelligent sleeve", which can adapt to any medication packaging and shares adherence data with the HCP via Bluetooth connectivity,[24] are both in the early stages of evaluation.

CONNECTDROP (BIOCORP), the "connected MEMS," is a novel MEMS consisting of 2 components: a dose monitoring device (the "add-on") connected to a smartphone App ("the App") through Bluetooth transmission. The connected MEMS is designed to cultivate and sustain clinically significant therapeutic adherence in patients with glaucoma (Fig 1).

The CONDORE Pilot study aimed to evaluate the acceptability of the connected MEMS in a small cohort of patients with glaucoma, along with the App’s reliability in reporting data in real-time. The primary objective was to report the global satisfaction score of participants after using the device for 9 weeks. Additional secondary objectives were to describe any learning curve associated with using the connected device and characterize patient adherence after 8 weeks. Finally, patient and physician satisfaction with the connected device’s features and the patient’s ability to handle the device were evaluated. Safety objectives were met by collecting IOP and visual acuity (VA) data. The outcomes of this proof-of-concept pilot study will be used to assess the feasibility of a larger-scale clinical efficacy trial.

Methods

The CONDORE pilot clinical trial was a prospective, single-arm, single-center study conducted at the Center d’Ophtalmologie Blatin, Clermont Ferrand, France ("the investigation center"). The clinical trial is registered at ClinicalTrials.gov (NCT04552964). The study design was approved by the Comité de Protection des Personnes Nord-Ouest IV, Centre Hospitalier Régional Universitaire de Lille and approval was granted on February 20, 2020 (EudraCT/ID-RCB: 2019-A03193-54; N° Dossier (SI): 19.12.23.57958). The study was conducted in accordance with the International Council of Harmonization recommendations of Good Glinical Practice (ICH E6 R2), and the study protocol complied with the tenets of the declaration of Helsinki. Two study investigators (J.D.B. and E.A.), who are board-certified Ophthalmologists, were responsible for selecting patients who met the inclusion criteria and conducted all in-person study visits at the investigation center. A single qualified optometrist carried out all clinical ophthalmic examinations. Administrative staff at the investigation center undertook one visit ("Visit 2"), a phone consultation.

Eligibility Criteria

Study participants were recruited from patients treated for glaucoma at the investigation center. Inclusion criteria were as follows: age >18 years of either sex with clinically confirmed glaucoma, who were on topical multitherapy for bilateral glaucoma, including fixed combination, preservative-free dorzolamide and timolol (Dualkopt, Laboratoires Théa) at the standard dose of 1 drop each eye twice daily. Patients eligible for participation were also required to be adherent to their medication, as judged by their ophthalmologist and supported by clinical assessment, including a normal intraocular pressure (IOP) <18 mm Hg. Furthermore, the study participants had to be comfortable handling a smartphone and engaging with smartphone applications.

Patients were not considered for the study if they met any of the following exclusion criteria: they had an additional ophthalmic disease that required concurrent treatment; a history of ocular hypersensitivity, uveitis, and/or infectious ophthalmic disease; they had undergone ocular surgery in the previous 3 months or ocular surgery is planned in the next 3 months; where best correct visual acuity (BCVA) is less than 20/70 in the better seeing eye; patients who do not instill their own topical medication; patients with alcohol-dependency and/or are heavy smokers; are not capable of understanding the study protocol or giving informed consent; the patient is known to be nonadherent to their medication; the patient is enrolled in another clinical trial; the patient is subject of a regulatory order with detention in prison, a psychiatric ward or other state institution; they are an employee of either the study center or the sponsor; the patient is not registered in the French healthcare system. The patient is female and is pregnant, breastfeeding, or of child-bearing age and not using a recognized form of contraception.

Study Design

Eligible patients were invited to participate in the study during a routine clinical check-up at the investigation center. Participants received an information sheet which explained the study’s aims, a description of the protocol, the benefits and risks associated with study participation, and a contact phone number. They were also informed of their right to withdraw their participation from the study at any point. At their discretion, the investigators could

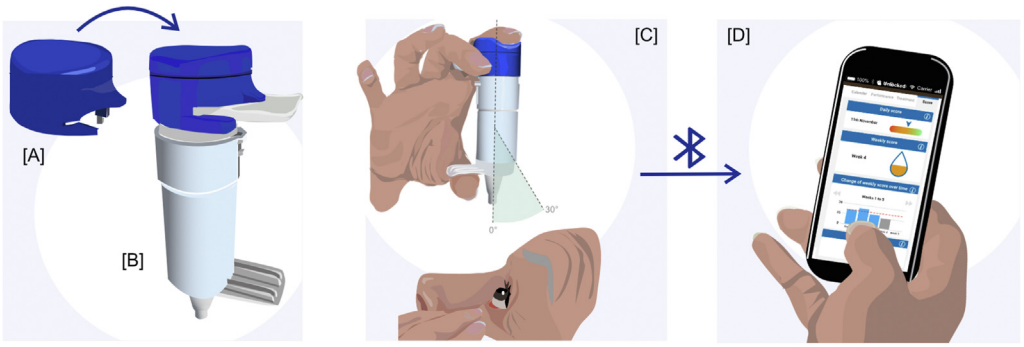

Figure 1. The CONNECTDROP connected MEMS (BIOCORP) for measuring treatment adherence in patients with glaucoma. The "add-on" (**A**) is configured to clip onto an ergonomic bottle of fixed combination dorzolamide/timolol (Easygrip, Laboratoires Théa) (**B**). The patient then uses the assembled system to deliver the prescribed dose of medication. The dotted lines and green triangle define the degree of angulation to the vertical required for a correct application technique (**C**). ✱ = Bluetooth wireless connection. MEMS = Medication Event Monitoring System.

withdraw patients from the study at any time. All patients enrolled in the study gave their signed informed consent to participate. As a pilot study, no power calculations were undertaken. However, a sample size of 30 was set based on logistical considerations at the investigation site and the intended duration of the study. A summary of the study timeline is shown in Figure 2.

The duration of the study was 9 weeks. This was designed to account for the 8 weeks that one 10 ml bottle of timolol/dorzolamide was expected to last, followed by 1 week of data collected after a bottle change to evaluate a key aspect of the device's usability. The study period started from the day that the participant was enrolled and underwent their baseline visit. Each participant was required to attend 3 study visits during the study. Visits 1 (baseline) and 3 (week 9) were in person with an investigator at the clinic. At visit 1, participants were provided with an individually numbered kit containing the following items: 2 bottles of 10 ml fixed combination timolol/dorzolamide and its product information leaflet, the add-on (pre-attached to 1 bottle), a smartphone with the App installed and linked to the add-on, a compatible phone charger, instructions for using the connected device, and a copy of the patient satisfaction questionnaire to complete and return at visit 3. Patients were also provided with the contact number to call the clinic to report any adverse events (AEs), and any technical problems were referred on to the project manager or Medical Director at Laboratoires Thèa. Visit 2 (week 8) was a telephone interview with the participant. A detailed list of study interventions and procedures can be found in Table S1.

Criteria were established for withdrawing patients from the study and were as follows: if the patient withdrew their consent to participate, the patient failed to follow the defined protocol, or any other reason it could jeopardize the participant's welfare or the integrity of the study. If a patient withdrew from the trial, an early withdrawal visit was scheduled at the study center (Fig 2). All cases of withdrawal from the study and their reasons were recorded. When the study material was returned by the participants at visit 3, the raw data obtained by the App from the Add-on were extracted for processing and analysis.

The Medication Event Monitoring System

The add-on used in this study was an internally powered, Bluetooth-enabled attachment that recorded 4 variables at each dosing event: the number of drops delivered, the date and time that each drop was delivered, whether the drop was delivered at the correct angle and for each 24-hour period, whether the correct interdose interval was observed (>8 hours). Although the add-on records every drop dispensed, the App is configured to process up to 2 drops per dosing event. Any count above 2 is processed as 2 drops. This allows for any dispensed drops which inadvertently miss the eye. The add-on was purpose-designed to attach to the upper part of an ergonomic bottle (Easygrip, Laboratoires THÉA, Clermont Ferrand) containing a 10 ml fixed combination preservative-free timolol/dorzolamide and was powered by a lithium button battery, which was expected to last for 12

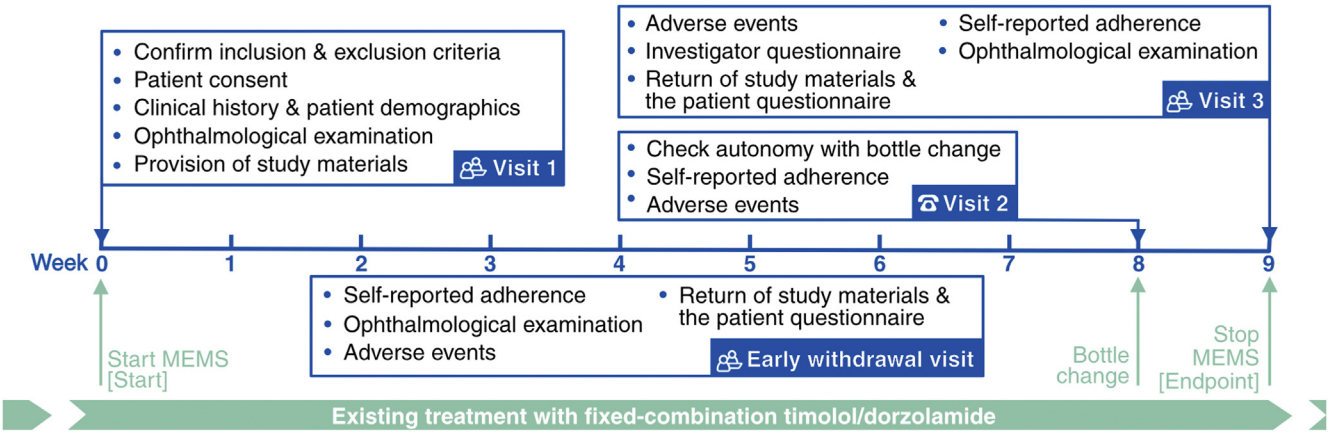

Figure 2. The CONDORE pilot timeline. Study participants attended the investigation center at baseline (week 0) and at the end of week 9 (or in the event of early withdrawal). Visit 2 was a phone consultation at which adherence and safety data were collected, and the patients reported their experience of changing the bottle. MEMS = Medication Event Monitoring System.

months with average use. Hardware version 0.92 was used in this study. When connected to the smartphone via Bluetooth, the add-on automatically transferred all stored data to the paired device, which was simultaneously deleted from the add-on. If the smartphone was out of range, the add-on could store data equivalent to 120 instillations.

The App is designed to be used exclusively with the connected add-on, and the software version 1.0.0 was used in this study. The data displayed on the user interface were current up to the most recent transfer from the connected add-on. The user interface of the App consists of 4 screens: "Calendar,",= "Performance," "Treatment," and "Score" (Fig S3). The raw data recorded by the add-on are displayed on the user interface as a series of composite measures, the "Daily," "Weekly," and "Global" scores from which the user can derive actionable feedback. The calculations used to generate the composite measures are detailed in Table S2. The add-on, together with the App, conforms to EU Medical Device Regulation (MDR [EU[2017/745), CE mark CE 0459 (Article 10 and 20). At the study endpoint, the data collected by the App were transferred securely via a certified data hosting service (EURIS, HEALTH CLOUD, Boulogne-Billancourt, France) for data processing.

Outcome Measures

The Patient Satisfaction questionnaire comprised 17 questions (PQ.01-17) spanning 5 domains: global satisfaction with the MEMS, experience using the App, self-reported adherence when using the MEMs, satisfaction with bottle handling with the add-on, and ease of changing the add-on to a new bottle. Answers were given using a 5-point Likert scale with terms adjusted to reflect agreement, likelihood, frequency, and performance, as appropriate, except for question 11 (PQ.11), which was semi-qualitative, and respondents were invited to provide a free text response. Qualitative data about the participant's attitude after using the device were also collected verbally at visit 3. Similarly, the investigators were required to fill out an investigator satisfaction questionnaire of 6 questions about how they perceived the connected MEMS affected each participant's adherence.

The primary objective of this study was to measure global patient satisfaction with the connected device, and the outcome measure for this was the qualitative response to the question, "How satisfied are you with the CONNECTDROP device?". The remaining 16 questions, along with the 6 questions of the investigator survey (InQ.01-06), were intended to provide outcome measures for the secondary objectives regarding patient satisfaction relating to handling the bottle with add-on connected, their experience of interacting with the App, and changing treatment bottles.

The patient learning curve was described by comparing the median values of medication drop number, proportion of dosing interval respected and correct and incorrect drop angles at baseline, at week 4, and week 8. Patient adherence was measured by analyzing the change of "raw" and "complete" scores, composite measures generated by the App for each 24-hour period at baseline, week 4, and week 8. The raw score is the sum of points awarded for correct minimum drop number and correct interdose interval, and the maximum daily raw score is 10. The complete score, accessible to participants by the App (as the "daily score," applies a factorial based on the bottle angle at each dosing event. A raw or complete score above 7 each day was considered adherent for the purposes of this study. At week 8, each participant was awarded 2 adherence scores, calculated as their mean raw and complete scores. The data were also tested for correlation between patient satisfaction and adherence scores. A participant's ability to successfully change the add-on to a new bottle was measured indirectly by the proportion who successfully returned a complete data set for week 9. A summary of all the composite measures used for the study is provided in Table S2. The study kits were assigned a random sequential number during posthoc analysis (generated using the www.random.org online tool) for data presentation for anonymization purposes.

Safety Endpoints

Safety outcome data were collected at visit 1, visit 2, visit 3, and premature withdrawal (where applicable). Adverse events were screened for at Visits 2 and 3. Participants could contact the investigation center at any point in the interim to report a possible adverse event.

Direct safety endpoints for the add-on are impossible to define. Therefore, clinical safety associated with the treatment drops was monitored as a proxy. Safety endpoints were the reporting of ocular and systemic adverse events by System Organ Class and preferred terms at visit 2 and visit 3, or premature withdrawal (where applicable) and participant access to an AE reporting line. Intraocular pressure and VA measurements were done at visit 1 and visit 3.

Statistical Methods

Descriptive statistical analysis was performed for all study data. The absolute and relative values of the positive responses to the 5-point Likert scale were reported for categorical data and were analyzed using either the McNemar or McNemar−Bowker test.

Continuous variables were summarized by reporting the mean, standard deviation, median, minimum, and maximum values. Where confidence intervals were given, they were 2-sided and set at the 95% level. Statistical significance was set at $P < 0.05$ and calculated using the parametric (paired t test) and nonparametric (Wilcoxon signed-rank test). Distributional assumptions were examined using the Kolmogorov−Smirnov or Shapiro−Wilk test before statistical analysis.

No imputations were performed to replace missing values, and no special treatment was given to outliers. Correlation between variables was tested using Spearman's rank correlation coefficient. All analyses were performed in RStudio (RStudio Team (2020). RStudio: Integrated Development for R. RStudio, PBC, Boston, MA) and/or IBM SPSS v.25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.).

Results

A total of 32 patients were approached to participate in the study. One patient was excluded because their glaucoma was monocular, and 31 patients were subsequently enrolled. Thirty patients returned a completed patient satisfaction questionnaire. The first participant's visit 1 was on September 25, 2020, and the final visit 3 was on April 27, 2021. All 31 patients completed the first visit, received a numbered study kit, and contributed to the intention-to-treat (ITT) analysis. Thirty participants completed the patient satisfaction questionnaire, and all patients completed the 3 visits required by the study protocol. Four participants had major protocol deviations that resulted in early withdrawal from the study. One participant discontinued their use of the connected device due to an unrelated AE (coronavirus disease 2019 infection). Two connected devices suffered a software malfunction that could not be rectified, and 1 further connected add-on broke. None of the devices associated with a major protocol deviation contributed data to the per-protocol set (PPS) analysis. There were 37 minor protocol deviations involving 23 participants (Table S3). Nine of the minor protocol deviations reported involved the 4 participants who had experienced a major protocol

deviation. None of the minor protocol deviations were considered of sufficient impact to affect the data quality, and consequently, there were 27 patients in the PPS. Participant flow during the study is summarized in Figure 4.

In the ITT cohort, 64.5% of patients were female, the mean (SD) age was 70.7 (0.8) years, and 67.7% of patients enrolled had been diagnosed with glaucoma for more than 10 years of the ITT group. A summary of participant demographics and clinical characteristics for ITT and PPS groups at baseline is provided in Table 4. A list of concurrent ophthalmic medications during the study period is accessible in Table S5.

At visits 2 and 3, 100% of patients in the PPS groups reported that they had been adherent to their medication. No protocol amendments were necessary during the study period. Apart from the patient demographics and safety data, the results reported here are based on data obtained from the PPS set.

Global Patient and Investigator Satisfaction

The primary outcome of the CONDORE study was global patient satisfaction. In response to the question, "How satisfied are you with CONNECTDROP® having used it for 9 weeks with your daily treatment?", 74.1% of participants from the PPS were satisfied or very satisfied (Fig 5). Thematic analysis of the reasons provided by the 7 participants who were not "very satisfied" or "satisfied" showed answers could be categorized as no perceived benefit (they considered themselves already competent with their medication), the connected device lacked an important function (a sound or light alarm when a dose was due), disappointment in the App functionality (the App was slow to update doses), or general practicality of integrating the connected device into their routine (always having to have the phone around). Correspondingly, the investigators' questionnaire results found that they were "satisfied" or "very satisfied" with the information provided by the connected device for 81.5% of their patients. Concerning the accessibility of the app, participants scored this highly, with 88.8% reporting that the App was "very easy" or "easy" to use, and 70.4% reporting that they had accessed it at least once daily. When asked about specific app screens, the response was more mixed, with 55.5% and 48.1% of participants stating that they "agreed" or "strongly agreed" that the "Calendar" or "Performance" screens helped with their treatment, respectively. Responses were also less favorable regarding the usefulness of the weekly (33.3%) and global scores (33.3%). Results for a question (PQ.06) that asked participants to rank the screens in order of usefulness have not been included as the question structure resulted in ambiguous responses. The investigators rated the usability of the App screens for the study participants highly, with positive views about 88.8% of participants for the "Treatment" screen to 77.7% for the "Score" screen, 81.5% for the "Calendar" screen, and 85.2% for the "Performance" screen. Participants felt that the MEMS helped them take their treatment more regularly (59.2%), but it was less helpful in preventing forgotten doses (33.3%). Although a minority of participants agreed that the add-on improved bottle handling (37.0%), 70.3% stated that they found the bottle with the add-on attached easy to use, and 74.1% of respondents said it was "easy" or "very easy" to change the add-on from bottle 1 to bottle 2. Figure 6 summarizes the participants' response to the patient satisfaction question 11, which asked them to indicate the benefits they perceived from the App. The most selected option was that it helps users pay more attention to how they instill their drops. The complete results for the participant and investigator surveys are found in Fig S7 and Fig S8.

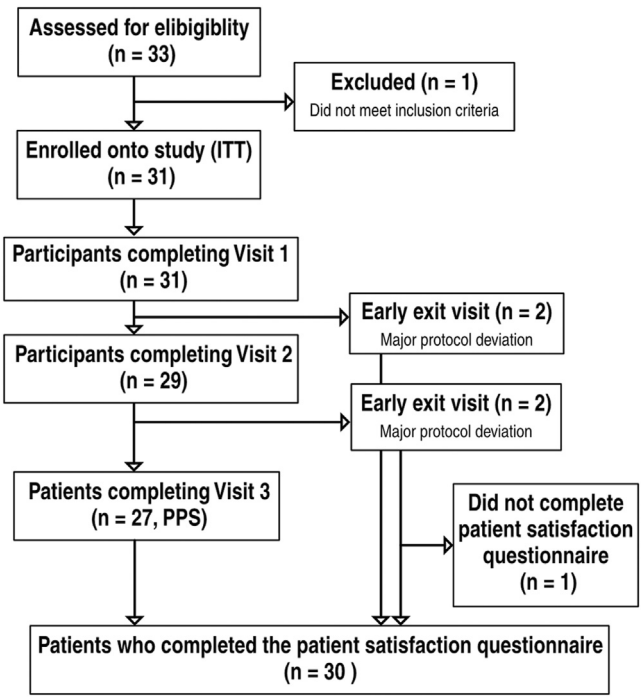

Figure 4. Participant flow diagram for the CONDORE pilot study. ITT = intention to treat.

The Patient Learning Curve.

The baseline median (range) average daily number of drops instilled in the PPS group was 5.4 (3.4−8.4). It was 4.1 (2.0−7.3) at week 4 and 4.4 (0.1−10.3) at week 8. The difference between the mean of the average drops dispensed at weeks 4 and 8 compared with baseline was significant ($P < 0.001$ and $P = 0.001$, respectively). However, no significant difference was detected between weeks 4 and 8 (Table 6a). The median 7-day percentage of respected time interval (8 hours) between morning and evening drops was 100% (85.7−100.0) at baseline, 100% (42.9−100.0) at week 4%, and 100% (0.0−100.0) at week 8. A significant difference in the mean 7-day percentage respected time was detected between week 8 and baseline ($P = 0.010$). No difference was found between baseline and week 4 and week 4 and week 8 (Table 6b). The median daily number of drops (7-day average) instilled with the correct inclination of the bottle was 4.6 (0.7−7.4) at baseline, 3.7 (0.0−6.0) at week 4, and 3.9 (0.0−7.6) at week 8 (Table 6c). There was a significant reduction in the drops delivered at the correct angle between baseline and week 4 ($P < 0.001$) and week 8 ($P = 0.002$) (Table 4). The median number of drops instilled at the incorrect angle was 1.1 (0.0−5.4) at baseline, 0.9 (0.0−5.1) at week 4 and 0.6 (0.0−5.9) at week 8. There was no significance detected in the differences between any time points (Table 6d).

Table 4. Participant Characteristics at Baseline

Variable	ITT	PPS
Sex n (%)		
Male	11 (35.5)	10 (37.0)
Female	20 (64.5)	17 (63.0)
Age		
Mean (SD), years	70.7 (8.0)	70.6 (8.6)
Range, years	50.0 − 83.0	50.0 − 83.0
Patients with a history of glaucoma or OHT in the family n (%)		
Yes	2 (6.5)	2 (7.4)
Years since glaucoma diagnosis n (%)		
<5	3 (9.7)	3 (11.1)
5−10	7 (22.6)	7 (25.9)
>10	21 (67.7)	17 (63.0)
Does the patient have other ocular clinical history apart from glaucoma? n (%)		
Yes	12 (38.7)	9 (33.3)
Does the patient have a systemic medical or surgical history? n (%)		
Yes	19 (61.3)	18 (66.7)
Has the patient had previous or current ocular treatment?* n (%)		
Yes	31 (100.0)	27 (100.0)
Does the patient experience ocular symptoms? (burning, stinging, eye treatment)?		
Yes	13 (41.9)	11 (40.7)
IOP, mmHg, mean (SD)		
Right eye	13.9 (2.5)	13.6 (2.5)
Left eye	14.0 (2.1)	14.0 (2.)
VA/10, mean (SD)		
Right eye	8.1 (2.9)	8.3 (2.6)
Left eye	9.0 (1.6)	9.0 (1.6)
RIGHT eye n (%)		
Fundus examination normal	29 (93.5)	26 (96.3)
Retinal detachment present	2 (6.5)	1 (3.7)
VF normal	20 (64.5)	9 (33.3)
LEFT eye n (%)		
Fundus examination normal	31 (100.0)	27 (100.0)
Retinal detachment	0 (0.0)	0 (0.0)
VF normal	17 (54.8)	16 (59.3)

IOP = Intraocular pressure; ITT = intention to treat; OHT = Ocular hypertension; PPS = per-protocol set; SD = standard deviation; VA = Visual acuity; VF = Visual field.
*A full summary of topical medications is summarized in Table SX.

Participant Adherence

The median daily raw score at baseline was 10.0 (6.3−10.0). Week 4 was 10.0 (6.0−10.0) and 10.0 (0.0−10.0) in week 8. The difference in daily raw scores at baseline and week 4 and week 8 was significant ($P = 0.032$ and 0.007, respectively). There was no significant difference between week 4 and week 8 (Table 7a). The median daily complete score was 9.4 (4.9−10.0) at baseline and 9.1 (3.6−10.0) at week 4, and 9.0 (0.2−10.0) at week 8. There was again a significant difference between baseline and week 4 ($P = 0.037$) and week 8 ($P = 0.010$), with no difference detected between week 4 and week 8 (Table 7b).

The median day participants first obtained a complete score >7 was 1.0 (1.0−12.0). The median length of the longest run of days where complete scores >7 was 10.0 (1.0−63.0; Table 7c). There was no correlation between raw and complete scores and the global satisfaction scores ($\rho = -0.209$ and −0.338, respectively; Table 8).

Posthoc analysis of the connected device data found that the overall proportion of the PPS group achieving a raw and complete score >7 for 80% or more of the first 8 weeks of the study period was 85.2% and 70.4%, respectively (Figs 9 and 10).

Responding to the question, "Do you think that CONNECTDROP helped you take your medication more regularly?" 59.2% answered that they "agreed" or "completely agreed" that the connected device helped them take their treatment more regularly. However, only 33.3% "strongly agreed" or "agreed" that it reduced the likelihood of forgetting to take the medicine (Fig S7).

Participant Ability to Change the Bottle.

A total of 74.1% of patients reported that changing the add-on to a new bottle was "easy" or "very easy," and there was high approval of the accompanying in-app video demonstrating the bottle change, with 70.3% finding it "satisfactory" or "very satisfactory" (Fig S7). Using data extracted from the connected devices, 11 devices (40.7%) had medication data recording interrupted at the beginning of week 9, coinciding with the change of bottles (Figs 9 and 10). This contrasted

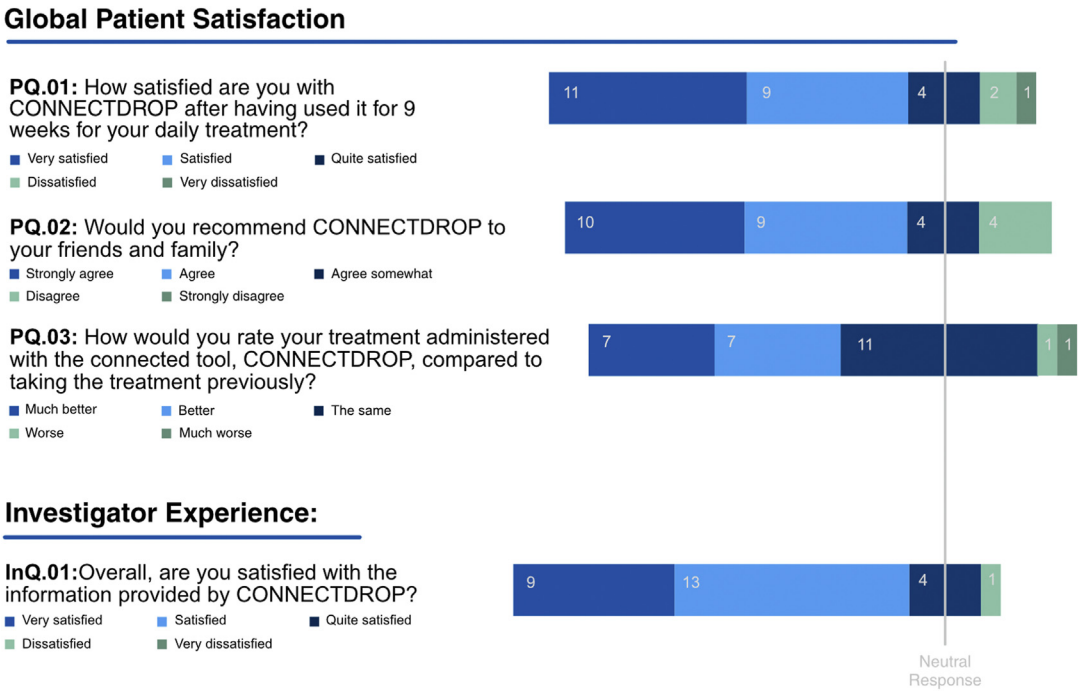

Figure 5. Results of questions 1–3 (PQ.01–03) of the participant satisfaction questionnaire and question 1 (InQ.01) of the investigator satisfaction questionnaire. Responses have been collected using a 5-point Likert scale. The numbers displayed in the boxes are the absolute number of responses for each answer.

with 7.4% of patients who reported that changing the bottle was "difficult" or "very difficult" (Fig S7). The responses of the 7 participants who did not find the bottle "easy" or "very easy" to change were analyzed for qualitative themes and difficulties changing the add-on to a new bottle, that changing the bottle "hurt my thumbs" or the participant felt inadequately instructed in using the connected device.

Safety Analysis

One non–treatment-related AE (coronavirus disease 2019 infection) was recorded, resulting in the participant's early withdrawal from the study. No serious AEs were reported. No major or minor treatment-related AEs were recorded. There were no significant differences between visual acuity of the left and right eye between baseline and visit 3 or IOP of the left and right eye between baseline and visit 3 (Table 9).

Discussion

This report presents the results of the CONDORE pilot study, which evaluated a novel MEMS device connected to a mHealth App to improve medication adherence in patients with glaucoma. Such a tool is currently not widely available to patients with glaucoma and their HCPs. This study aimed to assess the feasibility of a larger-scale efficacy trial by evaluating the acceptability and handling of the device to end-users (patients and HCPs) and the suitability of the data delivered by the device to measure medication adherence. The results indicated a high proportion of participants (74.1%) overall had a positive view of the connected device after 9 weeks. Similarly, the investigators reported that they considered the connected device beneficial for 81.5% of participants. Furthermore, using data from the connected devices, 85.2% of devices recorded a raw score of at least 7 on 80% or more of the first 8 weeks of the study period. The equivalent proportion achieving a complete score was 70.4%.

The primary study objective measure was global patient satisfaction with the connected MEMS. Data taken from the PPS cohort have shown that the connected MEMS has a high global satisfaction rating, with 74.1% of patients responding that they were either "satisfied" or "very satisfied" after their experience of using the connected device (Fig 5). No threshold for what is considered an acceptable level of global satisfaction has been defined for this study. However, these satisfaction rates are comparable to those reported in other studies on mHealth Apps in chronic diseases, including hypertension,[25,26] cardiovascular disease,[27] and rheumatoid arthritis,[28] where reported user satisfaction was high.[22] We believe that this pilot trial has demonstrated sufficient acceptability among target users to justify a more extensive scale efficacy trial.

Investigator satisfaction with the MEMS was similarly high. The 2 study investigators "agreed" or "strongly agreed" that they were satisfied with the information provided by the MEMS for 81.5% of the participants in the PPS. This is encouraging, as negative HCP attitudes to mHealth interventions are a barrier to their uptake. Safi and colleagues have characterized HCP attitudes to "eHealth," where the concerns documented include an impact on their professional autonomy in patient care and a negative effect on the quality of physician–patient

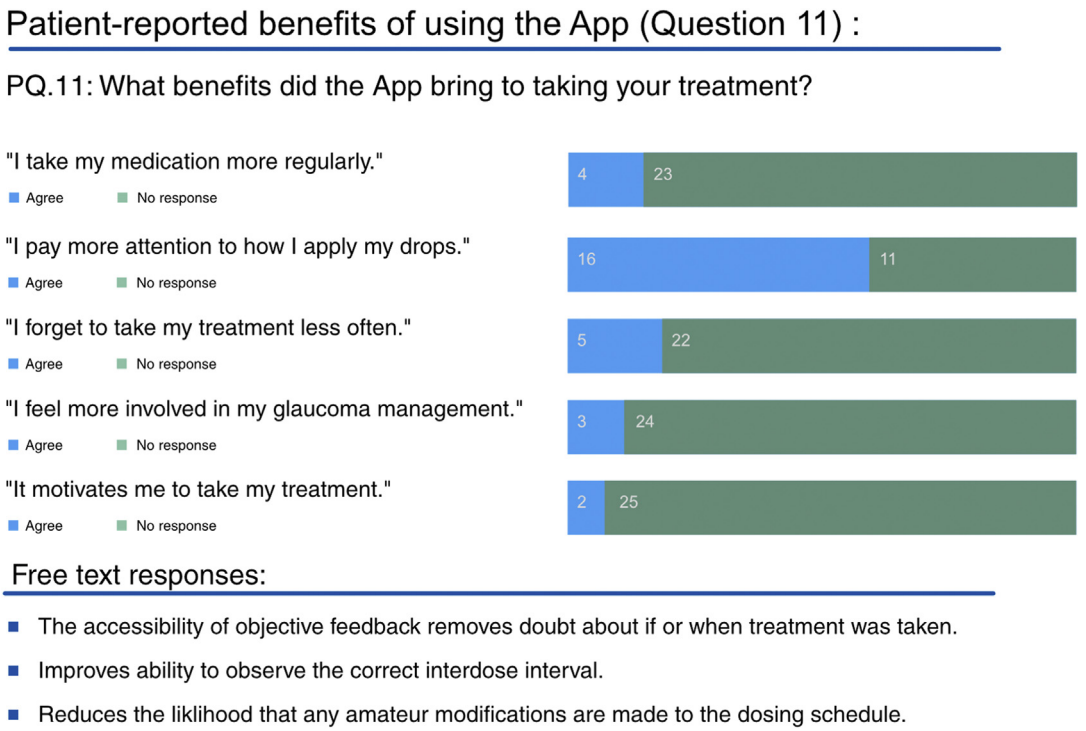

Figure 6. Results for participant satisfaction questionnaire question 11 (PQ.11), which asked respondents to circle one or more prepared statements on benefits associated with the App which they felt applied them. This question also allowed participants to provide a free text response to the PQ.11. Four responses were recorded, 3 of which are paraphrased here (the fourth was a duplicate of one of the 5 original statements).

interaction.[29] Our pilot study found that the investigators regarded the connected device as easy to use and would recommend the MEMS to their patients. They also reported that the information generated by the App makes it easier to discuss medication and health management with patients (70.4% of cases). Suboptimal patient−HCP communication is a recognized barrier to medication adherence in patients with glaucoma.[5] We speculate that any tool facilitating this communication will positively impact adherence. However, investigators indicated that the connected device improved treatment in only 55.6% of participants (Fig S8). We suspect that this is because this assessment was for a cohort of patients experienced in instilling eye drops and that they were already considered adherent. We therefore hypothesize this score would be higher in a nonadherent or newly diagnosed patient population. However, this would need to be confirmed in a future study.

The proportion of raw and complete scores >7 over the 8-week study period was reported for each device and threshold of 80% was used in this study as the benchmark for adherence. In the CONDORE pilot trial, 85.2% and 70.4% of devices reached this threshold for raw and complete scores, respectively. One of the main challenges associated with measuring adherence in topical glaucoma treatment is that no standardized threshold for clinically

Table 6a. Descriptive Statistics for Median Number of Drops Instilled at Baseline, Week 4 and Week 8. Based on Data Recorded on Days 1 to 7 (Baseline), on Days 22 to 28 (week W), and on Days 50 to 56 (Week 8)

Timepoint	N	Mean	SD	Median	Range	*P*-Value
Baseline	27	5.8	1.2	5.4	(3.4 −8.4)	**<0.001** (Week 4) **0.001** (Week 8)
Week 4	27	4.4	1.0	4.1	(2.0−7.3)	**<0.001** (Baseline) 0.145 (Week 8)
Week 8	27	4.7	1.7	4.4	(0.1−10.3)	**0.001** (Baseline) 0.145 (Week 4)

P < 0.05 are indicated in bold.
SD = standard deviation.

Table 6b. Descriptive Statistics for the Proportion (%) of Daily Interdose Intervals, Which Respects the Prescribed Interval (>8 hours). Based on Data Recorded on Days 1 to 7 (Baseline), on Days 22 to 28 (Week 4), and on Days 50 to 56 (Week 8)

Timepoint	N	Mean	SD	Median	Range	*P*-Value
Baseline	27	97.9	5.2	100.0	(85.7−100.0)	0.063 (Week 4) **0.010** (Week 8)
Week 4	27	92.1	15.0	100.0	(42.9−100.0)	0.063 (Baseline) 0.311 (Week 8)
Week 8	27	88.9	20.7	100.0	(0.0−100.0)	**0.010** (Baseline) 0.311 (Week 4)

P < 0.05 are indicated in bold.
SD = standard deviation.

Table 6c. Descriptive Statistics for the Average Daily Number of Drops Instilled at the Correct Bottle Angle. Based on Data Recorded on Days 1 to 7 (Baseline), on Days 22 to 28 (Week 4), and on Days 50 to 56 (Week 8)

Timepoint	N	Mean	SD	Median	Range	*P*-Value
Baseline	27	4.2	2.0	4.6	(0.7−7.4)	**<0.001** (Week 4) **0.002** (Week 8)
Week 4	27	3.0	1.8	3.7	(0.0−6.0)	**<0.001** (Baseline) 0.283 (Week 8)
Week 8	27	3.2	2.1	3.9	(0.0−7.6)	**0.002** (Baseline) 0.283 (Week 4)

$P < 0.05$ are indicated in bold.
SD = standard deviation.

meaningful adherence in this group of patients has been defined. However, the consensus in glaucoma treatment is that patients are adherent if they take 80% of treatment as prescribed,[30] and this was the rationale for adopting that threshold in our study. The main challenge to interpreting the results is that apart from self-reported adherence at visits 2 and 3, the connected device was not validated. Therefore, confirming whether a nonadherent (or adherent) event is due to true nonadherence or other cause, such as device malfunction, is difficult. For example, devices C05, C09, C19, and C37 all recorded periods (>48 hours) in which no dose was recorded (Figs 9 and 10). This was despite the respective participants reporting that they had been adherent. Similarly, device C20 had raw and complete scores of less than 7 for most of the trial period. Raw data analysis suggested that this was because only 1 drop was instilled at each dosing event, contrary to the prescription and was unexplained. This could be due to genuine nonadherence (such as forgetfulness, avoiding treatment in a painful eye, or difficulty handling the treatment bottle). Furthermore, patients with glaucoma will likely overreport their adherence,[31] and participant self-reported adherence will have had some inherent unreliability. Conversely, it could be due to device malfunction. To correct this uncertainty in a future study design, we would adopt a supplementary, objective method of recording medication events in tandem with the device and implement data integrity checks during the study.

Despite this limitation, the data collected by the connected devices provided some intriguing insights into the adherence characteristics of this study cohort. Most recorded 2 or more drops being instilled across all dosing events (Figs 9 and 10), indicating study participants were overall highly consistent with instilling the correct drop number at the correct time intervals. The most common reason a connected device reported nonrespect of the dosing interval (less than 8 hours interdose interval) was a missed dose. Seventeen devices in the PPS group (63.0%) recorded at least 1 missed dose during the study period. Forgetting to take a dose is one of the most common causes of nonadherence in patients with glaucoma.[8] Only 3 of the 231 (1.3%) dosing events reported as nonrespect of the dosing interval were genuine (out of 3402 dosing events in the PPS), with 1 dose being given only 9 minutes early.

The difference between the raw and complete scores is a proxy measure for the bottle angle at installation. Four (14.8%) connected devices (C02, C05, C06, and C13) had "adherent" raw scores but "nonadherent" complete scores at 8 weeks. Furthermore, a significant drop in the percentage of doses given using the correct bottle angle was recorded between baseline and week 4 and week 8 (Table 6c). The evidence for the clinical significance of the angle of the bottle to treatment outcomes is lacking, and the bottle angle at installation is not listed as a factor in poor installation technique.[32] Moreover, instillation technique is probably less important than the dose and timing of treatment.[4] This has highlighted the importance of developing composite measures where the influence of the individual variables used is proportionate to the clinical effect (rather than adherence, per se), as far as that is understood. On this basis, it could be argued that the bottle angle variable has too much weighting on the complete score and participants who were not observing the correct angle—which may disproportionately affect patients with reduced manual dexterity—are, in fact, not experiencing worse clinical outcomes. As this evidence comes to light, it will be necessary for developers of mHealth systems to update the composite measures used to process raw data accordingly. For this study, whether the raw or complete score is more appropriate to use as a measurement for adherence will need to be determined for future research.

The presence of a substantial learning curve associated with using the device itself could be a potential barrier to being adopted by the patient. Data from the connected devices were analyzed to determine if a learning curve existed in this experienced cohort of patients. We used the following variables to compare for statistically significant changes between time points: drop number, the percentage days where the dosing interval was respected, correct bottle angle, raw score, and complete score to provide evidence of either a learning curve or, conversely, proof of performance degradation. The significant difference in drop number at baseline compared with weeks 4 and 8 (Table 6a) is artefactual as several drops are dispensed when the bottle is first used ("priming"). We conclude that there was no

Table 6d. Descriptive Statistics for the Average Daily Number of Drops Instilled at the Incorrect Angle. Based on Data Recorded on Days 1 to 7 (Baseline), on Days 22 to 28 (Week 4), and on Days 50 to 56 (Week 8)

Timepoint	N	Mean	SD	Median	Range	*P*-Value
Baseline	27	1.6	1.6	1.1	(0.0−5.4)	0.286 (Week 4) 0.706 (Week 8)
Week 4	27	1.4	1.6	0.9	(0.0−5.1)	0.286 (Baseline) 0.703 (Week 8)
Week 8	27	1.4	1.7	0.6	(0.0−5.9)	0.706 (Baseline) 0.703 (Week 4)

SD = standard deviation.

Table 7a. Descriptive Statistics for Average Weekly Raw Score (PPS). Based on Data Recorded on Days 1 to 7 (Baseline), on Days 22 to 28 (Week 4), and on Days 50 to 56 (Week 8)

Timepoint	N	Mean	SD	Median	Range	*P*-Value
Baseline	27	9.7	0.8	10.0	(6.3–10.0)	**0.032** (Week 4) **0.007** (Week 8)
Week 4	27	9.3	1.2	10.0	(6.0–10.0)	**0.032** (Baseline) 0.514 (Week 8)
Week 8	27	9.1	2.0	10.0	(0.3–10.0)	**0.007** (Baseline) 0.514 (Week 4)

$P < 0.05$ are indicated in bold.
PPS = per-protocol set; SD = standard deviation.

significant difference over time in the number of drops instilled, and the add-on had little or no impact on the participant's ability to instill the correct dose. There was also a significant decrease in the proportion of doses given with the correct dosing interval between baseline and week 4 (Table 6b). However, as described here, most events that the device reported as an incorrect dose interval were missed doses. Therefore, we believe there was no change in the proportion of days where the dose interval was respected.

We used the raw and complete scores to demonstrate a small but statistically significant drop in the population mean scores between baseline and week 4 and week 8 (Tables 7a and 7b). Although this may suggest a reduction in adherence associated with the device, an alternative explanation is that this may be evidence of "white-coat" adherence observed in patients in the lead-up to and immediately after a consultation with their HCP.[5] The magnitude of the fall in performance scores is small, and both means remain above the adherence threshold, so we suspect this does not reflect a sustained degradation of adherence scores. However, it highlights the need for a longer-term study using the connected device to confirm this. The average length of studies looking at the impact of mHealth on chronic disease is 6 months.[33] Overall, the statistical analysis results were as anticipated in this cohort of patients: experienced in the self-administration of topical eye treatment using the ergonomic bottle and a learning curve associated with using the device was not detected.

The final objective of this study was also to measure the usability of the MEMs device in this population, which, as a group of older patients, will be diverse in their manual dexterity, cognitive abilities, and overall autonomy. We consider the patient's ability to change the add-on to a new treatment bottle fundamental to the connected device's suitability for its required function. The patient questionnaire found that 14.8% of participants reported it was "difficult" or "very difficult" to change the add-on to a new bottle. However, our data show that 11 devices, C01, C04, C06, C07, C11, C16, C17, C18, C19, C21, and C26 (40.7%; Figs 9 and 10) stopped recording data at the time of the scheduled bottle change. This indirectly indicates that the add-on change for these devices was unsuccessful, although other potential causes must be ruled out. It was beyond the scope of this study to characterize events of week 9 in detail; however, based on participant self-reported adherence at the end of week 9, it is suspected that patients were continuing to administer their treatment, unaware that the add-on was incorrectly positioned. This indicates a handling issue to address before embarking on a longer-term trial by reviewing the instructions given to participants or a design review. A longer-term study must monitor bottle changes to ensure continuous data collection at this critical point. In addition, a recent upgrade to the software now means that users will receive a push notification if the App has not received data from the add-on for 72 hours.

One disappointing conclusion of our analysis was user satisfaction with the App. Although participants indicated that the App was easy to use (88.9%) and 70.4% reported engaging with it at least once daily, only 55.6% agreed that the calendar screen helped them with their medication schedule, and 48.1% agreed that the performance screen helped with the instillation technique (Fig S7). Furthermore, only 33.3% reported finding the weekly or global scores useful. As an adherent patient cohort, it is possible they did not require or value the feedback provided by the App. However, suboptimal accessibility and engagement with the App could reduce the efficacy of the connected MEMS in a cohort of newly diagnosed or nonadherent patients. It is also notable how participant satisfaction with the App compares with that of investigators, highlighting the connected device's dual function: on the one hand, it can provide HCPs with detailed clinical data about their patient's adherence, with the patient passively using the add-on. However, for the patient to proactively access the App for feedback on their adherence and then consciously change their behavior based on the feedback requires a level of engagement with the App, which this study suggests may have been lacking. Once again, this cohort's extensive treatment experience with treatment may be a factor and engagement with the App may be greater in a nonadherent patient population. Nevertheless, despite their exponential growth, mHealth Apps have suboptimal download rates and user "stickiness".[17] To improve the App's acceptability to users, it will be important to consider concepts such as "gamification".[17] More research is needed to understand better how mHealth Apps can overcome known barriers to App engagement to improve medication adherence.[33] Improvements to the App

Table 7b. Descriptive Statistics for the Average Weekly Complete Score (PPS). Based on Data Recorded on Days 1 to 7 (Baseline), on Days 22 to 28 (Week 4), and on Days 50 to 56 (Week 8)

Timepoint	N	Mean	SD	Median	Range	*P*-Value
Baseline	31	8.7	1.5	9.4	(4.9–10.0)	**0.037** (Week 4) **0.010** (Week 8)
Week 4	27	8.2	2.1	9.1	(3.6–10.0)	**0.037** (Baseline) 0.627 (Week 8)
Week 8	27	8.1	2.3	9.0	(0.2–10.0)	**0.010** (Baseline) 0.627 (Week 4)

$P < 0.05$ are indicated in bold.
PPS = per-protocol set; SD = standard deviation.

Table 7c. Descriptive Statistics: The Average Time to Achieving a Raw Score >7 and Duration That was Maintained for

Variable	N	Mean	SD	Median	Range
Day which first raw score ≥7 recorded.	27	1.5	2.1	1.0	(1.0–12.0)
Number of days where this score was maintained.	27	24.0	24.8	10.0	(1.0–63.0)

SD = standard deviation.

since the pilot trial have included a motivating push notification when the patient has achieved a good adherence score the previous 7 days.

This study reported no AEs related to patient safety. Three (9.7%) study devices failed or broke, resulting in participant withdrawal. Details for underlying reasons were not recorded. We intend to collect this information in future studies to ensure that any modifications to the add-on can be made to improve robustness. Clinical safety data found no significant change in IOP and Visual acuity in either eye over the study period (Table 9). However, a borderline *P*-value for VA in the left eye was approaching statistical significance. To ensure adequate safety surveillance, the power calculation of a future study will be sufficient to confirm a difference if it exists in future studies.

We have identified several limitations in the design of this study, which may have increased the risk of bias and reduced the generalizability of the results. One limitation is that the patient and investigator satisfaction questionnaires did not use standardized questionnaire tools. Although this does impact the reliability of the conclusion of the primary objective, for the purposes of this feasibility study, it does not change the outcome. However, we recognize that this level of uncertainty would not be tolerable to record patient reported outcomes in an efficacy trial and so future study design would use validated tools which incorporated the patient's interaction with the App, such as the mHealth Usability Questionnaire,[34] as well as treatment and adherence in glaucoma patients, such as the Eye-Drop Satisfaction Questionnaire.[35] The patients were from a single urban eye care hospital in France, and the results here may not generalize to other groups of patients. Furthermore, ethnicity and socioeconomic data were not collected, reducing the results' generalizability. For patients with glaucoma, this is of particular interest, as ethnicity and educational attainment is a risk factor for low adherence.[6,36] Collection of data regarding concurrent

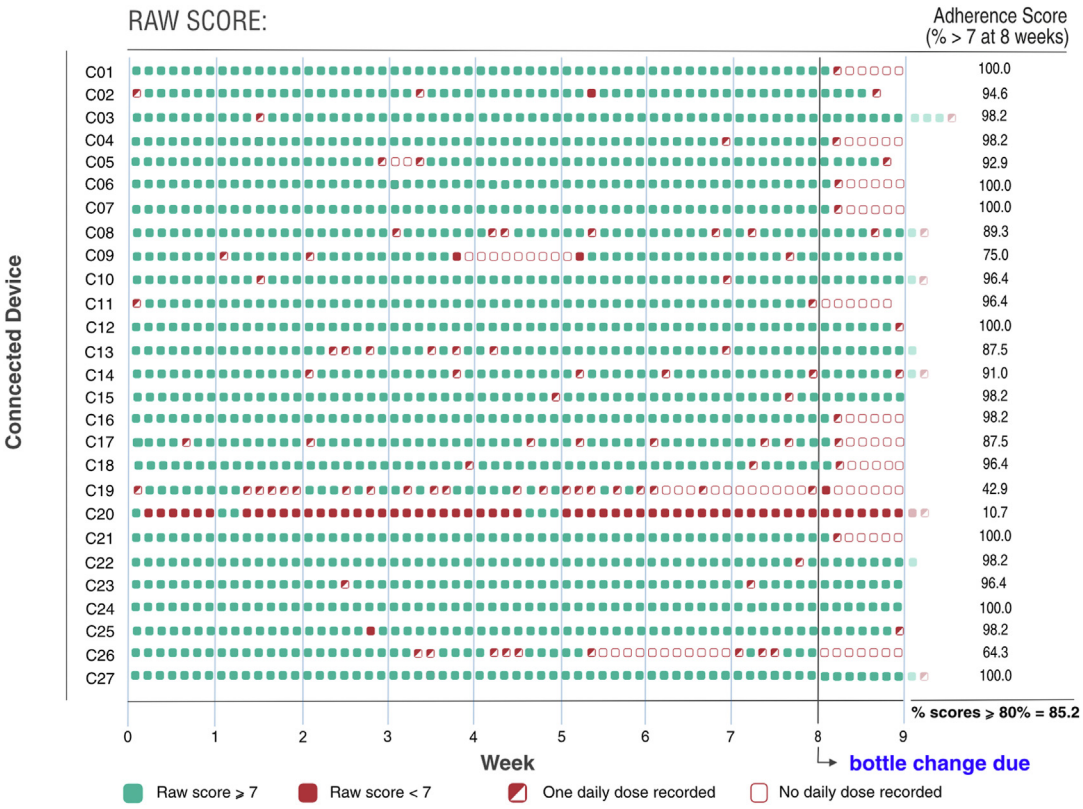

Figure 9. Data matrix of the raw scores recorded by each connected device used over the 9-week trial period, to include a bottle change event on or around the end of week 8 (day 56). The overall adherence score for each device is calculated at the end of week 8. Opaque data points were recorded after week 9 and were not included in the analysis.

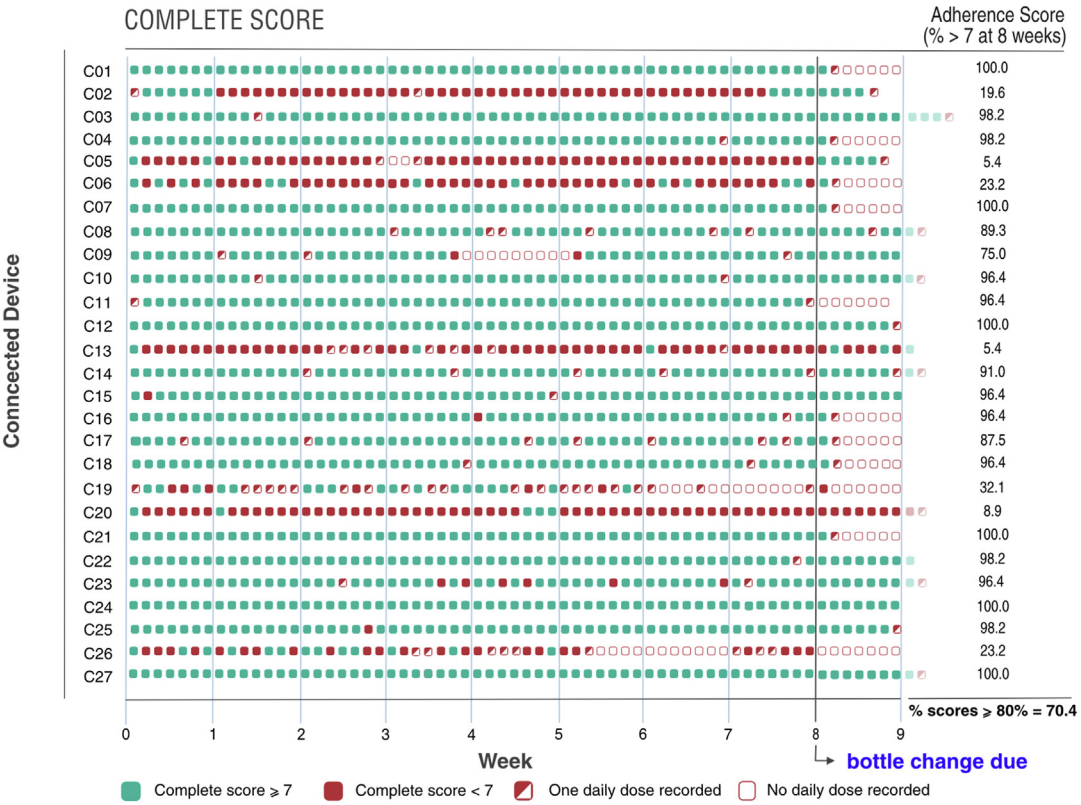

Figure 10. Data matrix of the complete scores recorded by each connected device used over the 9-week trial period, to include a bottle change event on or around the end of week 8 (day 56). The overall adherence score for each device is calculated at the end of week 8. Opaque data points were recorded after week 9 and were not included in the analysis.

medications, such as eye drops containing preservatives, was also limited. In future studies, this will be fully evaluated as this could influence how patients use the device. Participants were not stratified according to the severity of their glaucoma, so subgroup analysis on approval of and ability to use the app could not be undertaken. Indeed, the inclusion criteria selected for patients with glaucoma with relatively well-preserved visual acuity. This enabled the device performance to be evaluated without being confounded excessively by patient factors. However, future studies will need to provide for assessment with a diverse range of visual abilities to best understand who this device is likely to benefit and plan for accessibility measures. This study also limited inclusion criteria to patients with glaucoma, excluding patients with ocular hypertension. However, we recognize that patients with intraocular pressure (OHT) represent a large cohort who would benefit from this connected device and would look for ways to include them in future studies. For study recruitment, "adherence" was not explicitly defined, meaning that the study cohort may be more diverse in their adherence than intended. Furthermore, as discussed here, the connected add-on has not been validated to ensure that the parameters defined here are accurately measured, meaning that interpretation of objective data was prone to ambiguity. However, this

Table 8. Spearman's Correlation of Raw Score and Complete Score With Questions From Patient Satisfaction Domain (PQ.01-03)

Variable	Questionnaire Item	*P*-Value	ρ
Raw Score	PQ.01: How satisfied are you with CONNECTDROP® after having used it for 9 weeks for your daily treatment?	0.297	−0.209
	PQ.02: Would you recommend CONNECTDROP to your friends and family?	0.460	−0.148
	PQ.03: How would you rate your treatment administered with the connected tool, CONNECTDROP, compared to taking the treatment previously?	0.460	−0.149
Complete Score	PQ.01: How satisfied are you with CONNECTDROP® after having used it for 9 weeks for your daily treatment?	0.085	−0.338
	PQ.02: Would you recommend CONNECTDROP to your friends and family?	0.126	−0.302
	PQ.03: How would you rate your treatment administered with the connected tool, CONNECTDROP, compared to taking the treatment previously?	0.958	0.011

Table 9. Descriptive Statistics on Visual Acuity and IOP Results for the Right and Left Eye of the ITT Group for Adverse Event and Safety Analysis

Timepoint	N	Mean	SD	Median	Range	*P*-Value
Visual acuity/10 (right eye)						
Baseline	31	8.1	2.9	10.0	0.0–10.0	0.271
Week 9	31	8.0	3.0	10.0	0.0–10.0	
Visual acuity/10 (left eye)						
Baseline	31	9.0	1.6	10.0	4.0–10.0	0.082
Week 9	31	8.0	3.0	10.0	0.0–10.0	
IOP (right eye)						
Baseline	31	13.9	2.5	14.0	8.0–17.0	0.610
Week 9	31	14.1	2.7	15.0	8.0–18.0	
IOP (left eye)						
Baseline	31	14.0	2.1	14.0	10.0–18.0	0.707
Week 9	31	13.8	2.5	14.0	10.0–17.0	

IOP = intraocular pressure; ITT = Intention to treat; SD = standard deviation.

study used an ergonomic bottle that is calibrated for drop delivery, which mitigates this somewhat. Finally, the connected device, as with all MEMS, only measures adherence indirectly. It cannot determine whether the dispensed drop has reached the cornea. We are not aware of any noninvasive device that is capable of measuring this. This, however, to our knowledge, is the only MEMs which provides the patient with real-time feedback on their drop instillation and will potentially improve adherence through improving patients' motivation and confidence.

Glaucoma patients are well connected, with up to 80% accessing the internet and smartphone technology.[37] This connected device is intended to help patients with glaucoma measure their adherence as they go about their daily lives. Furthermore, the information provided by the App can help HCPs identify barriers to adherence in the individual patient as part of a precision medicine approach. A recent systematic review of interventions to improve adherence in glaucoma patients found no studies that link an intervention to reduced visual field loss,[38] confirming a knowledge gap in the management of glaucoma. The results of this CONDORE pilot study support the feasibility of the CONDORE efficacy trial, which will aim to demonstrate a link between the connected MEMS device to improved adherence and improved clinical outcomes.

Summary

This pilot study has shown that the connected device is acceptable to adherent patients with glaucoma and HCPs as part of their daily treatment regime. The data obtained from the connected devices provided insights into participant adherence at an individual and cohort level. However, a lack of validation challenges the reliability of the data, which will need to be addressed in future studies. With some exceptions, the overall adherence recorded in this cohort was high. Participants reported the device as easy to use, and this was supported by a lack of evidence of a learning curve. There was unanticipated evidence that changing the device to a new medication bottle may not have been successful in a significant minority of cases. Moreover, participant satisfaction with the App was suboptimal, which could adversely affect engagement and patient ability to action feedback given by the App. The outcomes of this pilot study have confirmed the feasibility of using the connected device for a larger-scale efficacy trial, with some modifications to both the add-on and the App indicated.

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Footnotes and Disclosures

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Disclosures:

All authors have completed and submitted the ICMJE disclosures form.

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HUMAN SUBJECTS: Human subjects were included in this study. The study design was approved by the Comité de Protection des Personnes Nord-Ouest IV, Centre Hospitalier Régional Universitaire de Lille and approval was granted on February 20, 2020 (EudraCT / ID-RCB: 2019-A03193-54; N-54; N3-54; N; 19.12.23.57958). The study was conducted in accordance with the International Council of Harmonization recommendations of good clinical practice (ICH E6 R2), and the study protocol complied with the tenets of the declaration of Helsinki. All patients enrolled in the study gave their signed informed consent to participate.

No animal subjects were used in this study.

Author Contributions:

Conception and design: Dériot, Albertini

Analysis and Interpretation: Dériot, Albertini

Data collection: Dériot, Albertini

Obtained funding: Dériot, Albertini

Overall responsibility: Dériot, Albertini

Abbreviations and Acronyms:
AE = adverse event; **BCVA** = best correct visual acuity; **OHT** = ocular hypertension; **HCP** = health care providers; **IMD** = Investigational Medical Device; **IOP** = intraocular pressure; **ITT** = intention to treat; **MEMS** = Medication Event Monitoring System; **PPS** = per-protocol set; **VA** = visual acuity.

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