British Journal of Ophthalmology

Original Research: Clinical Science

TITLE

Acceptability, adherence, and economic analyses of a new clinical pathway for the identification of non-responders to glaucoma eye-drops: A prospective observational study

AUTHORS

Heather A. Waterman, PhD[1], Simon M. Read, PhD[1], James E. Morgan, DPhil[2], David Gillespie, PhD[3], Claire Nollett, BSc[3], Davina Allen[1], PhD, Marjorie Weiss, DPhil[4], Pippa Anderson, PhD[5]

AFFILIATIONS

[1] School of Healthcare Sciences, Cardiff University; [2] School of Optometry and Vision Sciences, Cardiff University; [3] Centre for Trials Research, Cardiff University, [4] School of Pharmacy and Pharmaceutical Sciences, Cardiff University, [5] Swansea Centre for Health Economics, Swansea University

CORRESPONDING AUTHOR

Dr Simon Read; 12.14 Eastgate House; Cardiff University; 35-43 Newport Road; Cardiff, CF24 0AB;

E-mail: readsm@cardiff.ac.uk Tel: 02920 688930

WORD COUNT

2,887 (exc. Title Page, Precis, Abstract, Tables, Figures, Declarations and References)

PRECIS

A novel clinical pathway offered valuable non-response and adherence insights at minimal costs and appeared acceptable to patients. It has since been amended to address organisational concerns over a perceived rigidity in its appointment layout.

ABSTRACT

Background/Aims: To assess whether a new clinical pathway for glaucoma (Cardiff Model of Glaucoma Care, CMGC) was acceptable to patients and healthcare professionals and whether it provided novel clinical information on non-responsiveness and non-adherence to latanoprost ocular hypotensive treatment.

Methods: A single arm non-randomised prospective observational study incorporating newly diagnosed glaucoma / ocular hypertension patients. To assess issues of acceptability, qualitative observation and semi-structured interviews were conducted with patients and healthcare professionals. To determine clinical responsiveness, intraocular pressure was measured before and four hours after a clinician-instilled eye-drop over two distinct appointments separated by four weeks. Adherence data was collected through a Medicine Event Monitoring System and economic analyses were carried out comparing costs between novel and standard care pathway.

Results: Of 72 patients approached, 53 entered the study (74.3%) and 50 completed all study procedures (94.3%) suggesting acceptability. Intraocular pressure reduced more than 15% in 83 out of 92 study eyes by final visit (90.2%). Non-response rate to latanoprost was 5.1% having minimised the variable of adherence. During 1,376 observed days, eye-drops were instilled as prescribed on 1,004 occasions (73.0%), over-instilled on 137 days (9.9%) and not instilled on 235 days (17.1%). The Cardiff Model of Glaucoma Care provoked negligible costs, although healthcare professional acceptability varied.

Conclusions: The Cardiff Model of Glaucoma Care was introduced successfully, offering novel clinical and adherence insights at marginal costs while acceptable to patients. However, healthcare

professionals felt that four-hour and four-week follow-up appointments could cause administrative problems. A streamlined version of the pathway has been developed to offer greater user discretion.

INTRODUCTION

Xalatan (latanoprost) is often prescribed as first-line eye-drop medication for treatment of glaucoma, the leading cause of permanent blindness worldwide. [1] As a prostaglandin lowering intraocular pressure (IOP) by increasing uveoscleral outflow, it has a demonstrable record of efficacy and safety since its first availability in 1996. [2] However, some patients do not respond to latanoprost with an ongoing debate in glaucoma literature about actual non-response rates (online supplementary table 1). When patients present in outpatient clinics with higher-than-expected IOP despite being prescribed ocular hypotensive eye-drops, the physician is faced with a dilemma because IOP is a product of i) the patient's physiological response to the eye-drops (pharmacogenetics) and ii) a patient's level of adherence to eye-drops (behaviour). [3-4] Current clinical pathways do not usually distinguish between pharmacogenetics and behavioural elements of IOP. Physicians commonly assume poor response rather than poor adherence, adding alternate or additional medication to obtain the desired IOP reduction. This approach is illogical without knowing whether the patient is responsive to medication or their adherence level. Furthermore, this can adversely affect the outcome if adherence is an issue, since adherence rates tend to fall with more complex medication regimes. [5-6] Generally, the decision is based on physician estimate of adherence, often gathered from interactions within clinical consultations, which is known to be inaccurate. [7-8] With little done formally in clinics to differentiate pharmacological from behavioural effects on treatment responsiveness, the feasibility of identifying non-responders in routine glaucoma clinics and the impact of adherence behaviour on response to eye-drops requires demystifying. This study explored these issues through a new clinical pathway (Cardiff Model of Glaucoma Care, CMGC) looking to reduce over-treatment or surgery. We undertook feasibility, adherence, acceptability and economic analyses to determine whether it would be possible and useful to test for patients' non-response rates in the clinical setting.

MATERIALS & METHODS

The study had the following objectives:

1. To recruit glaucoma patients who were shortly to commence eye-drop treatment and process them through the CMGC;
2. To estimate the proportion of participants who receive the CMGC as intended;
3. To describe components of the intervention that were not received as intended, and reasons why (participant refusal, non-attendance, health professional deviation);
4. To estimate variability in IOP at the various time points;
5. To estimate the proportion of responders to eye-drop treatments;
6. To describe variation in participants' adherence to eye-drop therapy in the four weeks between the initial and follow up visit;
7. To estimate key resource use;
8. To estimate key cost implications of the CMGC.

Study design, setting, sample, sample size

This was a single arm non-randomised prospective observational study with primary data collection (ISRCTN ID:75888393). Ethics Committee approval was obtained from West Midlands – Black Country Research Ethics Committee, IRAS Project ID: 232242. All participants were given study information sheets prior to obtaining written informed consent and all practices followed the guidelines of the Declaration of Helsinki. [9]

Participants were enrolled from four routine glaucoma clinics in Wales, UK. Patients were included if: aged 18 years or over; diagnosed with either primary open angle glaucoma (POAG), ocular hypertension (OH), pseudo-exfoliative glaucoma, IOP equal to or greater than 21 mmHg, or normal tension glaucoma (NTG); and on the point of being prescribed glaucoma eye-drops either for the first time or after a minimum period of four weeks' discontinuation. Patients were excluded if they had any other physical conditions that might affect drop efficacy, such as severe arthritis or a disability.

It was proposed to recruit sixty patient participants, with this spread between all participating clinics. As this was an observational study, a formal a priori power calculation was not possible. [10] However, recruiting 60 participants would provide a level of precision around a 95% confidence interval. For example, if 80% of participants received the CMGC as intended, the 95% confidence interval could be estimated within +/- 10% (i.e. 70 to 90%). The widest the 95% confidence interval would be, if the estimated percentage was 50%, is +/- 13%.

Primary outcome measures were whether patients and glaucoma HCPs would accept the CMGC format and whether, clinically, non-response to latanoprost could be identified. Acceptability evaluation included data gathered from recruitment, appointment attendance and screening logs. We also used qualitative semi-structured interviews (patients, n=21, and glaucoma healthcare professionals (HCPs): doctors, optometrists, orthoptists and nurses, n=8), observations of 88 clinical consultations incorporating 50 patients and 10 healthcare professionals, as well as a further 52 field notes documenting administrative, logistical and organisational aspects to each site's implementation. These data provided insight into the acceptability of implementing the CMGC and how the protocol might be amended if necessary. All interviews were digitally recorded and transcribed verbatim.

Intervention - CMGC

Patients attended two extra clinic visits: i) within two weeks of diagnosis to initiate their treatment; and ii) four weeks later. Patients were informed of the purpose of the CMGC and given their IOP readings at each consultation. At the first visit, baseline pressures were measured using calibrated Goldmann Applanation Tonometers before an HCP instilled eye-drops and re-measured them four hours later. While research has indicated that latanoprost offers maximal effect eight to 12 hours post-instillation, Quaranta et al have noted IOP reductions at 2 hours. [11-12] As such, the four-hour gap between IOP measurements was selected based on balancing the practicality of receiving patients during core working hours, as well as the likelihood of clinical efficacy. At four weeks, the patient returned to have their IOP measured and another eye-drop instilled before again being asked to come back four hours later for IOP re-measurement. Based on the performance of their IOP over these

appointments, patients progressed through the CMGC algorithm towards a final outcome scenario, e.g. scenario A indicated patients were responsive to treatment within four hours of drop instillation and sufficiently adherent after four weeks to maintain a 15% drop in IOP from baseline (Figure 2). Patients were then informed of the outcome of the assessments and given follow-up appointments for their original clinic. This provided opportunity for non-responders to discuss alternative or additional treatment. The CMGC was conducted by a range of trained HCPs: physicians, optometrists, orthoptists and nurses and carried out in specialist, glaucoma clinics or general ophthalmology clinics.

Exposures, endpoints and other variables

A case report form collected all research data prospectively; this was completed by either nurses, optometrists, doctors or the research team. All patients were prescribed latanoprost as first-line treatment and, between the two hospital visits, all were instructed to instil the eye-drop at the same time each evening. All patients were given International Glaucoma Association booklets on glaucoma/ocular hypertension and advised to speak to their clinician if requiring further information.

With a primary outcome measure being whether non-response to latanoprost could be detected in clinic, we defined non-response to latanoprost as less than 15% reduction of baseline IOP. This provided assurance that IOP reduction is not related to diurnal variation and treatment is worthwhile. [13]

The following demographic/patient data were collected: age, sex, type of glaucoma, primary hand, ethnicity, nationality, postcode, length of time with eye condition, occupation, smoker and an ophthalmic assessment: anterior segment, gonioscopy, posterior segment, optic nerve imaging including optical coherence tomography, corrected visual acuity. We also monitored the presence of instillation site irritation, nasopharyngitis and other ocular adverse events.

To collect study adherence data, participants were asked to store their eye-drops within a container fitted with an electronic monitor in the lid (the Medication Event Monitoring System, MEMS), [14] retrieving their eye-drops from the bottle to take them each evening and replacing them afterwards.

Patients were not informed of the purpose of the bottle. We considered participants to have initiated treatment (following their first visit) provided that the container was opened at least once. 'Correct' implementation was defined as instilling eye-drops once per day. The MEMS bottles were study-specific data collection tools and not expected to be integrated more broadly into the CMGC pathway.

Health economics

To identify the required National Health Service (NHS) resources for the CMGC intervention as compared to standard glaucoma care, qualitative interviews, focus groups and observations were carried out in three of the four research sites.

Data management and statistical analyses

Statistical analysis: Continuous data were reported as means and standard deviations, or medians and interquartile ranges, as appropriate. Categorical data were reported as frequencies and proportions. All data were reported overall and separately for each glaucoma clinic. Outcomes were estimated with associated 95% confidence intervals. Using the MEMS [14] we estimated: i) the proportion of patients initiating their therapy after the first visit, [15] and ii) of those who initiated eye-drops, we estimated daily adherence using a two-level logistic regression model, accounting for repeated observations of days within individuals. The best fitting model, as indicated by Akaike's Information Criterion, was a random intercepts and random slopes model, with a linear time variable fitted as a random effect. For each adherence element, we explored variability across clinics, health boards, age, gender, and baseline IOP by including these as covariates in univariable regression analyses. We explored daily adherence separately for each of the CMGC responder types.

Health economics analysis: Data were costed and analysed using 2018's Unit Costs of Health and Social Care. [16] A sensitivity analysis was also undertaken to reflect differing staff combinations, ranging from the lowest costing qualified staff mix to a more costly, higher grade scenario. NHS resources involved in seeking additional clinical advice were also included in the analysis.

Qualitative data analysis: Qualitative data were analysed according to framework analysis, an explicit and systematic approach to qualitative data analysis [17-18].

RESULTS

Study Participants and Baseline Characteristics

Across the four research sites, 72 participants were screened between June 12, 2018 and March 21, 2019, providing 98 study eyes from 53 eligible participants (Figure 1). The study was active for each participant over a follow-up period of four to five weeks, recruiting for 40 weeks in total. Table 1 outlines the key demographic and condition-based characteristics of the patient sample by study eye.

Table 1: Baseline Characteristics of Participants by Study Eyes

Baseline Characteristics	Single Eye in Study	Two Eyes in Study	TOTAL
Total no.	8	45	53
Sex, no. (%)			
Male	5 (62.5)	24 (53.3)	29 (54.7)
Female	3 (37.5)	21 (46.7)	24 (45.3)
Ethnicity, no. (%)			
Asian	0 (0.0)	1 (2.2)	1 (1.9)
Black	0 (0.0)	3 (6.7)	3 (5.6)
White	8 (100.0)	40 (88.9)	48 (90.6)
Other	0 (0.0)	1 (2.2)	1 (1.9)
Clinic, no. (%)			
Clinic 1	5 (62.5)	27 (60.0)	32 (60.4)
Clinic 2	0 (0.0)	7 (15.6)	7 (13.2)
Clinic 3	0 (0.0)	6 (13.3)	6 (11.3)
Clinic 4	3 (37.5)	5 (11.1)	8 (15.1)
Age entering the study (years)			
Mean (standard deviation)	68 (SD: 6.4)	69 (SD: 10.6)	69 (SD: 10.0)
Median (range)	68 (57 – 78)	71 (45 – 91)	70 (45 – 91)
Eye condition, no. (%)			
*Normal Tension Glaucoma**	2 (25.0)	9 (20.0)	11 (20.8)
Ocular Hypertension	3 (37.5)	20 (44.4)	23 (43.4)
Primary Open Angle Glaucoma	3 (37.5)	16 (35.6)	19 (35.8)

* Normal Tension Glaucoma is detection of visual field loss in spite of IOP being lower than 21 mm Hg

After enrolment, three participants (six eyes) were withdrawn either through being lost to follow-up or due to adverse events. All other participants completed the study. Five adverse events were recorded (1 = cardiac issues, 1 = blurred vision, 3 = blepharitis) none of which were attributed to eye-drop instillation.

Clinical IOP Reduction

Table 2 outlines the baseline pre-treatment IOP mean for treated eyes, as well as average reductions in IOP following each visit. Data are available broken down by clinic in online supplementary table 2. Final IOP re-measurement (visit 2.2) demonstrated an average reduction from baseline of 34.2% in both right (SD: 15.4; Range: 12.7% increase – 65.3% reduction) and left eyes (SD: 13.7; Range: 3.4% reduction – 58.2% reduction). Table 2 also provides the number of responsive eyes established during each study visit, indicating that 83 of 92 study eyes (90.2%) ultimately saw a greater than 15% IOP reduction.

Table 2: Intraocular Pressure (IOP) and IOP Reduction in Study Eyes

Baseline IOP (mmHg)	**Right Eye**	**Left Eye**	**TOTAL**
No.	48	50	98
Mean (standard deviation)	22.8 (SD: 4.2)	23.0 (SD: 4.5)	22.9 (SD: 4.1)
Median (min. – max.)	22.5 (13.7 – 32.7)	22.7 (11.7 – 32.3)	22.2 (12.7 – 30.5)
Mean IOP Reduction from Baseline (%)	**Right Eye**	**Left Eye**	
Visit 1.2	21.3 (SD: 14.2)	24.9 (SD: 12.9)	
Visit 2.1	27.1 (SD: 16.2)	26.3 (SD: 14.1)	
Visit 2.2	34.2 (SD: 15.4)	34.2 (SD: 13.7)	
Eyes achieving >=15% IOP reduction	**Right Eye**	**Left Eye**	**TOTAL**
Visit 1.2 (n; %)	32 / 47; (68.1)	35 / 49; (71.4)	67 / 96; (69.8)
Visit 2.1 (n; %)	38 / 46; (82.6)	39 / 48; (81.3)	77 / 94; (81.9)
Visit 2.2 (n; %)	42 / 45; (93.3)	41 / 47; (87.2)	83 / 92; (90.2)

Regarding the CMGC algorithm and its associated clinical outcomes, most patients (56.1%) fell into scenario A, with the next largest group being those responding after four weeks who were non-responsive after four hours (scenario E; 18.4%). Those deemed non-responsive to treatment accounted for 5.1% of the sample (online supplementary table 3).

Participant Adherence to Eye-Drop Therapy

Valid electronic eye-drop use data were available for 48/53 (90.6%) of those participating. Three participants reported misusing the MEMS cap (e.g. not storing their eye-drops in the container) and a remaining two were lost to follow-up. Valid data were available for 1,536 potential dosing events over 1,376 days. For those participants providing valid data, all initiated eye-drop therapy. Of the 1,376 days observed, eye-drops were instilled as prescribed on 1,004 (73% of observed days) meaning

incorrect instillation on 372 days. Within individuals the percentage of adherent days ranged from 3.0% to 100%, and across centres there was minimal variation (online supplementary table 4). Where participants did not adhere on a given day, the primary indicator for this was the MEMS cap not being opened (63.2%, or 235/372 days). Instances of the MEMS cap being opened twice on the same day occurred 118/372 times (31.7%), and three, four, and five times occurred on 16, two, and one day respectively. Overall, there was no evidence of a difference in the odds of adhering over time (online supplementary table 5).

Variability in Four-Hour and Four-Week Assessments

The target of four-hour patient returns was largely met for both visits one and two (online supplementary table 6). The time between first and second visits were also recorded, the median deviation indicating most people returned after four and before five weeks. Those unable to return precisely four weeks after their initial visit reported other clinical appointments, holidays and lack of clinician availability.

Patient and HCP Acceptability of CMGC Intervention

Data collected from screening logs enabled initial assessments of patient acceptability (Figure 1). Of 72 eligible patients approached to participate, 53 agreed to take part (73.6%). For those declining, this was more commonly associated with arranging a CMGC appointment within the required timeframe, as opposed to regarding the CMGC as overly onerous. Additionally, once enrolled into the study most patients completed all study procedures (94.3%). During interview and observations, patients perceived the clinic to be worthwhile and were satisfied with their treatment. While those meeting certain criteria found it more difficult to become involved in the CMGC intervention, i.e. still being in employment, having daily commitments such as childcare, living an unmanageable distance from the hospital and so on, even for these patients the value of the approach was tangible (see Online Supplementary Table 7 for extracts from qualitative patient interviews and observations selected to represent a range of interviewees and research sites).

The clinical knowledge and data generated from the CMGC were perceived as extremely useful by HCPs with staff also expressing familiarity with the clinical procedures. A challenge felt across some sites related to logistical difficulties in implementation. This was predominantly around the requirement for four-hour and four-week follow-ups, which were difficult to incorporate administratively. However, some staff felt this effort would be worthwhile as the CMGC could potentially lead to better clinical and patient outcomes.

Health Economics: Standard Care vs. CMGC Costings

As derived by the 2018's Unit Costs of Health and Social Care, the additional costs of integrating CMGC into the health service ranged from \$11.20/£9* to \$22.40/£18*, with \$16.17/£13* being the most plausible marginal cost (see Online Supplementary Table 8). [16] Whilst the number of patients led to consumption of more staff resources, one clinic felt their model of consecutive glaucoma clinics (morning and afternoon) holding one reserved place per clinic had no meaningful impact on the workload nor for service provision. In services where glaucoma clinics were only held on half days this was not necessarily the case with staff availability and potential administrative burdens reported.

DISCUSSION

Our study demonstrates it is feasible to introduce a new way of working in glaucoma clinics identifying whether patients respond to glaucoma eye-drops. The sample size of 53 participants and 98 study eyes provided enough data for novel clinical IOP and adherence insights. Although recruitment was expected to be challenging based on patient-perceived burden of additional appointments, 73.6% of those approached entered the study and 94.3% of those completed all clinical procedures, suggesting broad acceptability.

In practice, the CMGC intervention was performed as intended with only occasional deviation in relation to appointment timings. Predominantly, these were patient-driven based on difficulties in attendance through holidays, other hospital appointments or general unavailability. In such cases, patients returned at an alternative time to complete their care pathway. The level of recruitment

between sites varied, with clinics 2, 3 and 4 each enrolling between 6 and 8 patients, while clinic 1 offered 32 patients. This was due to issues associated with site openings and closures over the study duration but was not felt to compromise the sample, instead offering exposure to a wider range of sites and research settings than originally intended. The estimated additional costs for hosting the CMGC visits were marginal, ranging from $11.20/£9* to $22.40/£18* per patient across the sampled sites. Depending on prevalence and clinical capacity, however, it is possible that scaling up the service to accommodate CMGC visits could increase the required number of clinic sessions.

Streamlining the CMGC intervention and identifying the core aspects that can be readily integrated into existing health board structures would address issues with HCP acceptability. Feedback from clinicians suggested the prescribed nature of the model negatively affected its implementation potential, a key problem being the four-weekly, rather than the more common six-weekly, appointments. We have adapted the CMGC (Figure 2) to maintain its key clinical functionality while reducing overly prescriptive aspects to offer smoother implementations. Additionally, we have identified that those patients achieving sufficient IOP reduction by visit 2.1 (scenarios A and E) need not attend visit 2.2 given that treatment efficacy and adherence are confirmed. Certainly, for those sites where these issues were deemed to be less problematic, the benefits of the intervention for clinical data, patient experience and tuition, as well as the potential for reduction of future appointments were felt to outweigh the logistical problems.

The non-response rate to latanoprost in our sample was 5.1% having minimised the confounding variable of whether patients were adhering or not. This result is line with previous research [19-21] that report rates of 4.1%, 13% and 21% respectively where adherence was controlled and the non-response rate cut-off point set at 15%.

Our study demonstrates that the relationship between response to treatment and adherence is complex. Past studies attempting to demonstrate the effect of an adherence intervention on IOP have neglected the impact of non-response to eye-drops on study outcomes. [22] Future studies on

adherence intervention effectiveness will need to take non-response to treatment into account. Reliance on IOP as the primary endpoint for effectiveness of adherence intervention studies is also questionable given there is no strong, discernible relationship between adherence as measured by the MEMS and IOP. These observations suggest that a change in the rate of field loss or similar clinical output may be more beneficial.

The MEMS has known reliability and validity limitations, not least, that it affected patient adherence behaviour given its white container can act as a memory aid. Several patients told us they did not store their eye-drops in it, so no data were collected on adherence for these patients. Some patients guessed the purpose of the MEMS and perceived it to be a 'spy bottle', possibly affecting its use. Finally, patients could have opened the MEMS each day but not instilled their eye-drops, or opened it multiple times each day but not instilled on every occasion. These issues could have affected the accuracy of the adherence data. However, in the absence of a gold standard measure it is the best available at present, and perhaps multiple measures should be employed to achieve a rounded picture of adherence.

One further discussion point relating to the MEMS is that the adherence data were collected once each patient had completed visit 2.2 after four weeks. This data was often used during patient interviews as a means of identifying potential causes for eye-drops being missed, resulting in reports of social activities, holiday transportation and general forgetfulness as barriers to adherence. While the MEMS were not intended for the CMGC pathway beyond the study, the real-time monitoring of adherence through such technology may be helpful for patient interactions around their own self-medication. There are considerable ethical issues related to adherence monitoring, though if this was framed as a negotiated educational exercise, it may offer an avenue to positively investigate and aid patient engagement with their treatment.

In conclusion, it was possible to identify patients not responding to latanoprost and thereby reconsider their treatment accordingly in routine glaucoma clinics. The non-response rate was 5.1% and

altogether patients instilled eye-drops as per their prescription on 73% of observed days. Patients understood the purpose of the CMGC and were overwhelmingly prepared to attend. HCPs valued the knowledge that was gained from the CMGC but the logistical impact and engagement with the CMGC in each clinic was dependent upon disruption to current workflows. The protocol for the CMGC has been amended in the light of staff feedback, making it easier to implement. The per patient cost of the CMGC was minimal ($16.17/£13*) but this might increase if new clinics were required to accommodate patients.

* All currencies were converted from GBP to USD on 16th September 2019.

FINANCIAL SUPPORT

This research was funded in full by the Health and Care Research Wales Research for Patient and Public Benefit fund, ref: RfPPB-16a-1296. The funding organization had no role in the design or conduct of this research.

CONFLICT OF INTERESTS

No conflicting relationship exists for any author.

ACKNOWLEDGMENTS

The research team would like to acknowledge the input of research nurse, Kathleen Price, as well as the administrative assistance of Marie Platt and Veronica Dunning.

REFERENCES

1. Cook C, Foster P. Epidemiology of glaucoma: what's new? *Canadian Journal of Ophthalmology* 2012, 47(3):223-226.

2. Bean GW, Camras CB. Commercially available prostaglandin analogs for the reduction of intraocular pressure: similarities and differences. *Survey of Ophthalmology*. 2008, 53(6): S69–S84.

3. Emerick G. Prostaglandin nonresponders. How common are they, and how should one proceed? *Glaucoma Today*. 2005, Jan/Feb: 25-27.

4. International Council of Ophthalmology (2016) ICO Guidelines for Glaucoma Eye Care, 1st Edition. http://www.icoph.org/downloads/ICOGlaucomaGuidelines.pdf Accessed 31st August 2019.

5. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic treatment: a review of literature. *Journal of Behavioural Medicine*. 2008, 31 (3): 213-224

6. Newman-Casey PA, Robin AL, Blachley T, Farris K, Heisler M, Resnicow K, Lee PP. The Most Common Barriers to Glaucoma Medication Adherence: A Cross-Sectional Survey. *Ophthalmology*. 2015, 122 (7): 1308-1316.

7. Curtis J, Cai Q, Wade S et al. Osteoporosis medication adherence: physician perceptions vs. patients' utilization. *Bone* 2013; 55: 1-6.

8. Parker C, Chen Z, Price M et al. Adherence to warfarin assessed by electronic pill caps, clinician assessment, and patient reports: results from the IN-RANGE study. *Journal of General Internal Medicine* 2007; 22: 1254-9

9. World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. *Journal of the American Medical Association*. 2013, 310 (20): 2194-2194.

10. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of current practice and editorial policy. *BMC Medical Research Methodology*, 2010, 10 (1): 67.

11. Quaranta L, Pizzolante T, Riva I, Haidich AB, Konstas AG, Stewart WC: Twenty-four-hour intraocular pressure and blood pressure levels with bimatoprost versus latanoprost in patients with normal tension glaucoma. *British Journal of Ophthalmology.* 2008, 92 (9): 1227-1231.

12. Russo A, Riva I, Pizzolante T, Noto F, Quaranta L: Latanoprost ophthalmic solution in the treatment of open angle glaucoma or raised intraocular pressure: a review. *Clinical Ophthalmology*. 2018, 2 (4): 897-905.

13. Choplin N, Bernstein P, Batoosingh A, Whitcup S, Bimatoprost/Latanoprost Study Group. A randomized, investigator-masked comparison of diurnal responder rates with bimatoprost and latanoprost in the lowering of intraocular pressure. *Survey of Ophthalmology*, 2004, 49 Suppl.1: S19-25.

14. Medamigo. *Medication Adherence Monitoring and Management* online. Available at: www.medamigo.com Accessed 31 August 2019.

15. Vrijens B, De Geest S, Hughes D et al. A new taxonomy for describing and defining adherence to medications. *British Journal of Clinical Pharmacology*, 2012, 73(5): 691-705.

16. Curtis, L., Burns, A. *Unit Costs of Health and Social Care 2018,* University of Kent, Canterbury: Personal Social Services Research Unit; 2018.

17. Ritchie J, Spencer L, O'Connor W. Carrying out qualitative analysis. In: Ritchie J, Lewis J (Eds). *Qualitative Research Practice*. London: Sage; 2005: 219-262.

18. Ritchie J, Spencer E. Qualitative data analysis for Applied Policy Research. In: Bryman A, Burgess RG (eds). *Analyzing Qualitative Data*. London: Routledge; 1994: 173-194.

19. Gandolfi S, Rossetti L, Cimino L, Mora P, Tardini M, Orzalesi N. Replacing maximum-tolerated medications with latanoprost versus adding latanoprost to maximum-tolerated medications: a two-center randomized prospective trial. *Journal of Glaucoma*, 2003, 12 (4): 347-53.

20. Susanna R, Giampani J, Borges A, Vessani R, Jordao M. A double-masked, randomized clinical trial comparing latanoprost with unoprostone in patients with open-angle glaucoma or ocular hypertension. *Ophthalmology*, 2001, 108 (2): 259-63.

21. Rossetti L, Gandolfi S, Traverso C et al. An evaluation of the rate of nonresponders to latanoprost therapy. *Journal of Glaucoma*, 2006, 15 (3): 238-43.

22. Waterman H, Evans J, Gray T, Henson D, Harper R. Interventions for improving adherence to ocular hypotensive therapy. *Cochrane Database of Systematic Reviews*, 2013, Apr 30; (4): CD006132. doi: 10.1002/14651858.CD006132.pub3.

FIGURE HEADINGS & LEGENDS

Figure 1: Consolidated Standards of Reporting Trials diagram demonstrating the patient and study eye flow through the Cardiff Model of Glaucoma Care appointment structure through to data analysis

Figure 2: Revised Cardiff Model of Glaucoma Care (CMGC) Intervention Algorithm

Key: IOP = Intraocular pressure; HCP = Healthcare professional