

This is an Open Access document downloaded from ORCA, Cardiff University's institutional repository:<https://orca.cardiff.ac.uk/id/eprint/130190/>

This is the author's version of a work that was submitted to / accepted for publication.

Citation for final published version:

Waterman, Heather , Read, Simon, Morgan, James Edwards , Gillespie, David , Nollett, Claire , Allen, Davina , Weiss, Marjorie and Anderson, Pippa 2020. Acceptability, adherence and economic analyses of a new clinical pathway for the identification of non-responders to glaucoma eye drops: a prospective observational study. *British Journal of Ophthalmology* 104 (12) , pp. 1704-1709. 10.1136/bjophthalmol-2019-315436

Publishers page: <http://dx.doi.org/10.1136/bjophthalmol-2019-315436>

Please note:

Changes made as a result of publishing processes such as copy-editing, formatting and page numbers may not be reflected in this version. For the definitive version of this publication, please refer to the published source. You are advised to consult the publisher's version if you wish to cite this paper.

This version is being made available in accordance with publisher policies. See <http://orca.cf.ac.uk/policies.html> for usage policies. Copyright and moral rights for publications made available in ORCA are retained by the copyright holders.



1 **British Journal of Ophthalmology**

2 **Original Research: Clinical Science**

3

4 **TITLE**

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

7

8 **AUTHORS**

9 Heather A. Waterman, PhD¹, Simon M. Read, PhD¹, James E. Morgan, DPhil², David Gillespie, PhD³,
10 Claire Nollett, BSc³, Davina Allen¹, PhD, Marjorie Weiss, DPhil⁴, Pippa Anderson, PhD⁵

11

12 **AFFILIATIONS**

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

16

17 **CORRESPONDING AUTHOR**

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

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

20

21 **WORD COUNT**

22 2,887 (exc. Title Page, Precis, Abstract, Tables, Figures, Declarations and References)

23 **PRECIS**

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

27 **ABSTRACT**

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

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

39 **Results:** Of 72 patients approached, 53 entered the study (74.3%) and 50 completed all study
40 procedures (94.3%) suggesting acceptability. Intraocular pressure reduced more than 15% in 83 out
41 of 92 study eyes by final visit (90.2%). Non-response rate to latanoprost was 5.1% having minimised
42 the variable of adherence. During 1,376 observed days, eye-drops were instilled as prescribed on
43 1,004 occasions (73.0%), over-instilled on 137 days (9.9%) and not instilled on 235 days (17.1%). The
44 Cardiff Model of Glaucoma Care provoked negligible costs, although healthcare professional
45 acceptability varied.

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

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

50 INTRODUCTION

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

73 MATERIALS & METHODS

74 The study had the following objectives:

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

86 *Study design, setting, sample, sample size*

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

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

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

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

113 *Intervention - CMGC*

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

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

131 *Exposures, endpoints and other variables*

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

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

140 ¹³

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

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

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

153 *Health economics*

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

157 *Data management and statistical analyses*

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

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

173 **Qualitative data analysis:** Qualitative data were analysed according to framework analysis, an explicit
174 and systematic approach to qualitative data analysis ¹⁷⁻¹⁸.

175 RESULTS

176 *Study Participants and Baseline Characteristics*

177 Across the four research sites, 72 participants were screened between June 12, 2018 and March 21,
 178 2019, providing 98 study eyes from 53 eligible participants (Figure 1). The study was active for each
 179 participant over a follow-up period of four to five weeks, recruiting for 40 weeks in total. Table 1
 180 outlines the key demographic and condition-based characteristics of the patient sample by study eye.

181 **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. (%)			
<i>Male</i>	5 (62.5)	24 (53.3)	29 (54.7)
<i>Female</i>	3 (37.5)	21 (46.7)	24 (45.3)
Ethnicity, no. (%)			
<i>Asian</i>	0 (0.0)	1 (2.2)	1 (1.9)
<i>Black</i>	0 (0.0)	3 (6.7)	3 (5.6)
<i>White</i>	8 (100.0)	40 (88.9)	48 (90.6)
<i>Other</i>	0 (0.0)	1 (2.2)	1 (1.9)
Clinic, no. (%)			
<i>Clinic 1</i>	5 (62.5)	27 (60.0)	32 (60.4)
<i>Clinic 2</i>	0 (0.0)	7 (15.6)	7 (13.2)
<i>Clinic 3</i>	0 (0.0)	6 (13.3)	6 (11.3)
<i>Clinic 4</i>	3 (37.5)	5 (11.1)	8 (15.1)
Age entering the study (years)			
<i>Mean (standard deviation)</i>	68 (SD: 6.4)	69 (SD: 10.6)	69 (SD: 10.0)
<i>Median (range)</i>	68 (57 – 78)	71 (45 – 91)	70 (45 – 91)
Eye condition, no. (%)			
<i>Normal Tension Glaucoma*</i>	2 (25.0)	9 (20.0)	11 (20.8)
<i>Ocular Hypertension</i>	3 (37.5)	20 (44.4)	23 (43.4)
<i>Primary Open Angle Glaucoma</i>	3 (37.5)	16 (35.6)	19 (35.8)

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

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

187 *Clinical IOP Reduction*

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

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

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

196

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

201 *Participant Adherence to Eye-Drop Therapy*

202 Valid electronic eye-drop use data were available for 48/53 (90.6%) of those participating. Three
 203 participants reported misusing the MEMS cap (e.g. not storing their eye-drops in the container) and a
 204 remaining two were lost to follow-up. Valid data were available for 1,536 potential dosing events over
 205 1,376 days. For those participants providing valid data, all initiated eye-drop therapy. Of the 1,376
 206 days observed, eye-drops were instilled as prescribed on 1,004 (73% of observed days) meaning

207 incorrect instillation on 372 days. Within individuals the percentage of adherent days ranged from
208 3.0% to 100%, and across centres there was minimal variation (online supplementary table 4). Where
209 participants did not adhere on a given day, the primary indicator for this was the MEMS cap not being
210 opened (63.2%, or 235/372 days). Instances of the MEMS cap being opened twice on the same day
211 occurred 118/372 times (31.7%), and three, four, and five times occurred on 16, two, and one day
212 respectively. Overall, there was no evidence of a difference in the odds of adhering over time (online
213 supplementary table 5).

214 *Variability in Four-Hour and Four-Week Assessments*

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

220 *Patient and HCP Acceptability of CMGC Intervention*

221 Data collected from screening logs enabled initial assessments of patient acceptability (Figure 1). Of
222 72 eligible patients approached to participate, 53 agreed to take part (73.6%). For those declining, this
223 was more commonly associated with arranging a CMGC appointment within the required timeframe,
224 as opposed to regarding the CMGC as overly onerous. Additionally, once enrolled into the study most
225 patients completed all study procedures (94.3%). During interview and observations, patients
226 perceived the clinic to be worthwhile and were satisfied with their treatment. While those meeting
227 certain criteria found it more difficult to become involved in the CMGC intervention, i.e. still being in
228 employment, having daily commitments such as childcare, living an unmanageable distance from the
229 hospital and so on, even for these patients the value of the approach was tangible (see Online
230 Supplementary Table 7 for extracts from qualitative patient interviews and observations selected to
231 represent a range of interviewees and research sites).

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

238 *Health Economics: Standard Care vs. CMGC Costings*

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

246 DISCUSSION

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

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

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

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

275 The non-response rate to latanoprost in our sample was 5.1% having minimised the confounding
276 variable of whether patients were adhering or not. This result is line with previous research¹⁹⁻²¹ that
277 report rates of 4.1%, 13% and 21% respectively where adherence was controlled and the non-
278 response rate cut-off point set at 15%.

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

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

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

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

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

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

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

315 FINANCIAL SUPPORT

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

319 CONFLICT OF INTERESTS

320 No conflicting relationship exists for any author.

321 ACKNOWLEDGMENTS

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

324 REFERENCES

325 1. Cook C, Foster P. Epidemiology of glaucoma: what's new? *Canadian Journal of Ophthalmology*
326 2012, 47(3):223-226.

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

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

- 331 4. International Council of Ophthalmology (2016) ICO Guidelines for Glaucoma Eye Care, 1st Edition.
332 <http://www.icoph.org/downloads/ICOGlaucomaGuidelines.pdf> Accessed 31st August 2019.
- 333 5. Ingersoll KS, Cohen J. The impact of medication regimen factors on adherence to chronic
334 treatment: a review of literature. *Journal of Behavioural Medicine*. 2008, 31 (3): 213-224
- 335 6. Newman-Casey PA, Robin AL, Blachley T, Farris K, Heisler M, Resnicow K, Lee PP. The Most
336 Common Barriers to Glaucoma Medication Adherence: A Cross-Sectional Survey. *Ophthalmology*.
337 2015, 122 (7): 1308-1316.
- 338 7. Curtis J, Cai Q, Wade S et al. Osteoporosis medication adherence: physician perceptions vs.
339 patients' utilization. *Bone* 2013; 55: 1-6.
- 340 8. Parker C, Chen Z, Price M et al. Adherence to warfarin assessed by electronic pill caps, clinician
341 assessment, and patient reports: results from the IN-RANGE study. *Journal of General Internal*
342 *Medicine* 2007; 22: 1254-9
- 343 9. World Medical Association. World Medical Association Declaration of Helsinki: Ethical Principles
344 for Medical Research Involving Human Subjects. *Journal of the American Medical Association*. 2013,
345 310 (20): 2194-2194.
- 346 10. Arain M, Campbell MJ, Cooper CL, Lancaster GA. What is a pilot or feasibility study? A review of
347 current practice and editorial policy. *BMC Medical Research Methodology*, 2010, 10 (1): 67.
- 348 11. Quaranta L, Pizzolante T, Riva I, Haidich AB, Konstas AG, Stewart WC: Twenty-four-hour
349 intraocular pressure and blood pressure levels with bimatoprost versus latanoprost in patients with
350 normal tension glaucoma. *British Journal of Ophthalmology*. 2008, 92 (9): 1227-1231.
- 351 12. Russo A, Riva I, Pizzolante T, Noto F, Quaranta L: Latanoprost ophthalmic solution in the
352 treatment of open angle glaucoma or raised intraocular pressure: a review. *Clinical Ophthalmology*.
353 2018, 2 (4): 897-905.

- 354 13. Choplin N, Bernstein P, Batoosingh A, Whitcup S, Bimatoprost/Latanoprost Study Group. A
355 randomized, investigator-masked comparison of diurnal responder rates with bimatoprost and
356 latanoprost in the lowering of intraocular pressure. *Survey of Ophthalmology*, 2004, 49 Suppl.1: S19-
357 25.
- 358 14. Medamigo. *Medication Adherence Monitoring and Management* online. Available at:
359 www.medamigo.com Accessed 31 August 2019.
- 360 15. Vrijens B, De Geest S, Hughes D et al. A new taxonomy for describing and defining adherence to
361 medications. *British Journal of Clinical Pharmacology*, 2012, 73(5): 691-705.
- 362 16. Curtis, L., Burns, A. *Unit Costs of Health and Social Care 2018*, University of Kent, Canterbury:
363 Personal Social Services Research Unit; 2018.
- 364 17. Ritchie J, Spencer L, O'Connor W. Carrying out qualitative analysis. In: Ritchie J, Lewis J (Eds).
365 *Qualitative Research Practice*. London: Sage; 2005: 219-262.
- 366 18. Ritchie J, Spencer E. Qualitative data analysis for Applied Policy Research. In: Bryman A, Burgess
367 RG (eds). *Analyzing Qualitative Data*. London: Routledge; 1994: 173-194.
- 368 19. Gandolfi S, Rossetti L, Cimino L, Mora P, Tardini M, Orzalesi N. Replacing maximum-tolerated
369 medications with latanoprost versus adding latanoprost to maximum-tolerated medications: a two-
370 center randomized prospective trial. *Journal of Glaucoma*, 2003, 12 (4): 347-53.
- 371 20. Susanna R, Giampani J, Borges A, Vessani R, Jordao M. A double-masked, randomized clinical
372 trial comparing latanoprost with unoprostone in patients with open-angle glaucoma or ocular
373 hypertension. *Ophthalmology*, 2001, 108 (2): 259-63.
- 374 21. Rossetti L, Gandolfi S, Traverso C et al. An evaluation of the rate of nonresponders to
375 latanoprost therapy. *Journal of Glaucoma*, 2006, 15 (3): 238-43.

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

379 **FIGURE HEADINGS & LEGENDS**

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

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

383 Key: IOP = Intraocular pressure; HCP = Healthcare professional