



## What influences persistence with medicines? A multinational discrete choice experiment of 2549 patients

Holmes, E.A.; Morrison, V.L.; Hughes, D.

### British Journal of Clinical Pharmacology

DOI:  
[10.1111/bcp.12971](https://doi.org/10.1111/bcp.12971)

Published: 01/08/2016

Peer reviewed version

[Cyswllt i'r cyhoeddiad / Link to publication](#)

*Dyfyniad o'r fersiwn a gyhoeddwyd / Citation for published version (APA):*  
Holmes, E. A., Morrison, V. L., & Hughes, D. (2016). What influences persistence with medicines? A multinational discrete choice experiment of 2549 patients. *British Journal of Clinical Pharmacology*, 82(2), 522-531. <https://doi.org/10.1111/bcp.12971>

#### Hawliau Cyffredinol / General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal ?

#### Take down policy

This is the peer reviewed version of the following article: "What influences persistence with medicines? A multinational discrete choice experiment of 2549 patients." which has been published in final form at <http://dx.doi.org/10.1111/bcp.12971>. This article may be used for non-commercial purposes in accordance with Wiley Terms and Conditions for Self-Archiving.

#### Take down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

1 **Title:** What influences persistence with medicines? A multinational discrete choice experiment of  
2 2549 patients

3

4 **Authors:** Emily AF Holmes<sup>1\*</sup> BA(Hons), MSc; Professor Valerie L Morrison<sup>2</sup> MA, PhD, CPsychol;  
5 Professor Dyfrig A Hughes<sup>1</sup> PhD, FFRPS, FBPhS, FLSW.

6 <sup>1</sup> Centre for Health Economics & Medicines Evaluation, Bangor University, UK; <sup>2</sup> School of  
7 Psychology, Bangor University, UK

8

9 \*Author for correspondence: Professor Dyfrig Hughes, Centre for Health Economics & Medicines  
10 Evaluation, Bangor University, Arduwy, Normal Site, Bangor, Gwynedd, LL57 2PZ

11 E-mail: [d.a.hughes@bangor.ac.uk](mailto:d.a.hughes@bangor.ac.uk) Telephone: +44 (0) 1248 38 2950

12

13 **Running title:** Influences on persistence with medications

14

15 **Keywords:** adherence, persistence, medications, discrete choice experiment, stated preference

16

17 **Word count:** 3551

18 **Number of figures:** 1

19 **Number of tables:** 4

20 **Appendices / Electronic supplementary material:** 2

21

22 SUMMARY

23

24 **Aim:** To examine patients' stated preferences to persist with medicines and to explore the influence of  
25 psychosocial and sociocognitive factors.

26

27 **Methods:** Community-dwelling, hypertensive patients recruited from 9 European countries were  
28 invited to complete a discrete choice experiment (DCE) with attributes for treatment benefits, mild yet  
29 common adverse drug reactions (ADR), rare but potentially life-threatening ADR and dosing  
30 frequency. Patients responded to the binary-choice of which medicine would they be most likely to  
31 continue taking. Data were analysed using a random effects logit model.

32

33 **Results:** 2549 patients from Austria (n=321), Belgium (n=175), England (n=315), Germany (n=266),  
34 Greece (n=288), Hungary (n=322), Netherlands (n=231), Poland (n=312) and Wales (n=319)  
35 completed the DCE. All attributes significantly influenced patients' stated preference to persist with  
36 medications ( $p < 0.05$ ). Patients were willing to accept decreases in treatment benefits of: 50.6  
37 percentage points (95%CI: 46.1-57.9) for a very rare (as opposed to rare) risk of severe ADR; 28.3  
38 percentage points (95%CI: 25.2-33.1) for a once-daily instead of twice-daily dosing; and 0.74  
39 percentage points (95%CI: 0.67-0.85) for a 1% point reduction in mild ADR. Models accounting for  
40 psychosocial and sociocognitive characteristics were significantly different from the base case.

41

42 **Conclusion:** Patients' intention to persist with treatment was associated with their willingness to trade  
43 potential benefits, harms, and dosing frequency. Psychosocial and sociocognitive factors influenced  
44 the extent of trading. The utility model may have value in assessing patients' likelihood of persisting  
45 with medicines, and to tailor treatment to maximise persistence.

46

47 What is known about this subject?

48 1. Persistence with medicines can be considered as an outcome of a conscious decision patients  
49 make about whether the continued taking of the medication will increase their utility

50 2. Discrete choice experiments of implementation of dosing have found that patients are willing to  
51 accept adverse events in exchange for increase benefit.

52 What this study adds

53 1. Within our multinational DCE, hypertensive patients' intentions to persist with medication were  
54 influenced by treatment benefit, harm and dosing frequency

55 2. Psychosocial and sociocognitive factors changed the extent to which trade-offs were made  
56 among these attributes

57 3. The findings may have value in assessing patients' likelihood of persisting with medicines, and in  
58 the development of adherence-enhancing interventions

59 INTRODUCTION

60 Medication adherence encompasses the processes of initiation, implementation of dosing and  
61 persistence [1]. Reduced persistence with prescribed treatment is prevalent, with median length of  
62 time between patients' initiation of treatment for chronic diseases and their last dose being typically in  
63 the order of 1 year [2], despite failure to continue treatment having a detrimental effect on health [3].  
64 Reasons for the premature discontinuation of medicines are varied, and include factors related to  
65 patients, such as their beliefs and socioeconomic characteristics; the condition and its treatment;  
66 healthcare professionals and health systems [3,4]. There is emerging evidence of the role of  
67 behavioural economic theories in explaining patients' choice to persist with their prescribed medicines  
68 [5]. This is based on a notion that persistence with medications may be an outcome of a decision  
69 patients consciously make about whether the continued taking of their medication will increase their  
70 utility [6]. That is, if patients' utility (satisfaction) is maximised through taking their medications, their  
71 likelihood of persisting increases; but conversely if patients maximise their utility by not taking their  
72 medications, they will discontinue treatment.

73 Patients' utility may be examined using stated preference techniques, such as the discrete choice  
74 experiment (DCE) [7]. DCEs are an attribute-based survey measure underpinned by a Lancasterian  
75 view of utility which contends that goods and services (or medicines in this case) can be described by  
76 their characteristics or attributes and that the utility yielded by a medicine is a function of its various  
77 attributes [8]. Choices reveal information about the relative importance of each attribute, willingness  
78 to trade them, and total utility which patients aim to maximise.

79 DCEs represent a particularly effective method of eliciting preferences regarding health processes  
80 and outcomes that have gained extensive use in several contexts, including patients' preferences for  
81 medicines [9,10], but few empirical studies have made specific reference to the process of adherence  
82 to medication [11-13]. Hauber et al [11] conducted a study of treatment preferences and adherence to  
83 oral glucose-lowering agents amongst individuals with type 2 diabetes and found that while patients  
84 were willing to accept some adverse events in exchange for better glucose control, stated adherence  
85 would reduce with increasing risk of weight gain or myocardial infarction. Using a choice-format  
86 stated-preference survey, Johnson et al. [12] identified severity of depressive episodes, weight gain  
87 and the cognitive effects of treatments for bipolar disorder to affect patients' likelihood to adhere.

88 The view that non-adherence may be considered a rational behaviour that reveals patient  
89 preferences, adds to more established health psychology research studies. Within health and social  
90 psychology there exist several theoretical frameworks and models for explaining variation in health-  
91 related behaviours, which can be applied to persistence with medications [14]. Sociocognitive theory  
92 assumes that persistence is motivated by outcome expectancies and goals (such as improved  
93 health), which are determined by individuals' attitudes and beliefs [15-17]. Models within  
94 sociocognitive theory that have been applied to persistence with medications include the Health Belief  
95 Model [18-19] and The Theory of Planned Behaviour [20]. In this context, the Health Belief Model  
96 postulates the likelihood of persistence is increased if the perceived threat of illness from sub-optimal  
97 persistence is high, the benefit of medicines-taking is greater than the barriers to medicines-taking,  
98 and cues to action (e.g. reminders) are in place. The Theory of Planned Behaviour suggests an  
99 individual's intention to persist with medication increases if the perceived consequences are high  
100 (attitudes towards behaviour and outcome expectancies are positive), they have strong positive  
101 beliefs about what others expect (perceived social norms); and they perceive a high level of personal  
102 control / self-efficacy with regards to persisting, even when facing barriers; this will depend on their  
103 perception of internal resources (e.g. knowledge) and external resources (e.g. social support).

104

105 A more dynamic link between cognitions, motivation and behaviour can be explored using self-  
106 regulation theory [21]. Self-regulation theory describes the individual as an active problem solver and  
107 describes the cognitive and behavioural process by which individuals monitor and adjust their  
108 medication taking as the perceived solution to the problem of illness and its consequences [17].  
109 Illness representations or beliefs, together with treatment beliefs, shape coping responses e.g.  
110 persistence with medications. Beliefs about a particular illness and state of ill health are thought to  
111 form around five domains: Identity: signs and symptoms; Timeline: ideas about the time-frame of a  
112 condition (acute, chronic, cyclical); Cause: perception of cause (internal, external, stable, unstable  
113 etc.); Consequences: expected outcomes (physical, psychological and social); and, Control / cure:  
114 beliefs about potential cure and (internal/external) control. The contribution of the models described  
115 can be measured using self-report questionnaires for each component e.g. Barriers in the Theory of  
116 Planned Behaviour, or Illness consequences within Illness Perception Questionnaire.

117 Concurrent assessment of influences on patients' decisions to persist with a medication in terms of  
118 the utility they derive from medication characteristics, and theory driven psychosocial characteristics  
119 associated with medication preferences, increases the possibilities for interventions which could be  
120 both medicine and person-based. We are unaware of any study in which a range of health  
121 psychology theories have been tested simultaneously alongside preference elicitation methods in  
122 relation to medication persistence.

123 This study aims to (i) assess how patients from across Europe value the key attributes of medicines in  
124 their stated decision to persist with taking them and to examine the trade-off between potential  
125 benefit, harm and convenience; (ii) explore the relationship between these preferences and  
126 psychosocial and sociocognitive characteristics.

127

## 128 METHODS

129 The study involved a multi-national, web-based survey of hypertensive adult patients containing a  
130 DCE designed to elicit the preferences of patients for attributes of a hypothetical medication. The  
131 survey was piloted and ethically approved for eleven European countries: Austria, Belgium, England,  
132 France, Germany, Greece, Hungary, Netherlands, Poland, Portugal, and Wales. Patients were  
133 eligible for the study if they self-reported as being 18 years or older, diagnosed by a doctor as having  
134 hypertension that lasted at least 3 months, currently prescribed antihypertensive medication, and  
135 personally responsible for administering their medication. Respondents were excluded if they were  
136 aged less than 18 years, declared a psychiatric disorder, or lived in a nursing home or similar facility  
137 where they were not responsible for their own medicines taking. The target sample was for a  
138 minimum of 100 respondents per country (consistent with DCE studies [9,10]) up to a maximum of  
139 323 patients per country [22]. Respondents were principally recruited using advertisements in  
140 community pharmacies. Additional strategies included advertisements in hypertension clinics  
141 (Hungary), GP surgeries (Hungary and Poland) and local press (England and Wales). The survey  
142 was anonymous, hosted online and restricted to one respondent per Internet Protocol address.

143

144 DCE attributes, levels, and experimental design

145 We identified a list of potential attributes from 18 DCE studies of medicinal products identified in a  
146 systematic review [9]. Attributes identified were categorised as follows: mild adverse drug reactions  
147 (n=14 studies), treatment outcome (n=13), severe adverse drug reactions (n=6), dose related (n=5),  
148 duration of treatment (n=4), location of treatment (n=3), cost (n=3), route of administration (n=1),  
149 quality of life (n=1). The four most commonly used attributes were selected: treatment benefit, risk of  
150 common mild adverse drug reactions (ADRs), risk of rare but potentially life-threatening ADRs and  
151 dosage frequency (table 1).

152 We hypothesised that benefits would have a positive influence on patients' stated intention to persist  
153 with treatment, while increased risk of harms and dose frequency would be negative.

154 Insert Table 1 here

155 Each attribute was set to have three levels, representative of treatments used commonly for the  
156 management of chronic diseases. These were set at plausible values with a range sufficient to  
157 encourage respondents to trade, and limit potential dominance (Table 1), while allowing for scenarios  
158 (e.g. for improved benefit) to be modelled. For the DCE to be broadly generalizable across many  
159 common treatments, we used a hypothetical scenario of an unlabelled medicine and respondents  
160 were not given information on any specific condition or disease area. The question posed was: Which  
161 medicine would you be most likely to continue taking? Figure 1 provides an example of the pairwise  
162 choice used in the experiment.

163 Insert Figure 1 here

164 The number of possible choice scenarios in a full factorial design was  $3^4 = 81$ . As this would pose too  
165 great a burden on respondents, a fractional factorial design was selected with 9 profiles from a  
166 published design catalogue [23]. Binary choices were created using the fold-over method which  
167 replaces each attribute level with its opposite [24]. The attribute and question order was randomised  
168 to avoid left or right selection bias. Rational trading was tested by examining responses to a  
169 dominant profile which had a lower risk of mild ADR, lower dosage frequency, higher treatment  
170 benefit and lower risk of severe ADR.

171



172 Survey of psychosocial and sociocognitive factors

173 Validated self-report instruments were used to assess sociocognitive determinants of adherence [22].  
174 Illness representations were measured using the Brief Illness Perception Questionnaire (B-IPQ) [25].  
175 Patient beliefs in the necessity and concerns of medications were measured using the Beliefs about  
176 Medicines Questionnaire [26]. Constraints and facilitators of adherence were measured using barrier  
177 and social support subscales of the BRIGHT questionnaire [27-28]. Attitudinal and belief components  
178 of the Theory of Planned Behaviour (TPB) were scored on a 5-point Likert scale [29-30]. Self-  
179 reported adherence was measured using the Morisky questionnaire [31] which categorises  
180 participants as being non-adherent if they respond with a “yes” to at least one of four questions  
181 posed; and the Medication Adherence Rating Scale (MARS) which results in a continuous score for  
182 adherence (range 5-25) [32]. Details of the psychosocial measures used in the exploratory analysis  
183 are provided in Appendix 1. The full survey content is detailed elsewhere [22].

184

185 Translation

186 Measures that were not validated and available in the required language were translated into the  
187 appropriate languages (and back-translated for checks of compatibility with the English version) using  
188 accredited translators who were native speakers of the target languages and fluent in English.  
189 Descriptions of ADR prevalence were taken from the European Medicines Agency’s standard text for  
190 summaries of product characteristics, which is available in all European languages.

191

192 Data analysis

193 Results of the DCE were analysed in STATA (version 10; StataCorp LP, College Station, TX) using a  
194 random effects logit model that allowed for repeated observations from the same respondent:

195 
$$U = \beta_0 + \beta_1\text{SEVERE\_ADR} + \beta_2\text{DOSE} + \beta_3\text{BENEFIT} + \beta_4\text{MILD\_ADR} + \epsilon$$

196 U = utility derived by individual

197  $\beta_0$  = constant term

198  $\beta_i$  = estimated coefficient for each attribute (variable)

199  $\varepsilon$  = error term

200 Treatment benefit and risk of mild ADR were included in the analysis as linear continuous variables.

201 We explored the assumption of linearity for frequency of dose and risk of severe ADR, using effects

202 coding and plotting the resulting size of the coefficient against the level of each attribute. The level of

203 the base case was calculated using the estimated levels: e.g.

204  $\beta_{\text{very rare SEVERE\_ADR}} = - (\beta_{\text{rare SEVERE\_ADR}} + \beta_{\text{uncommon SEVERE\_ADR}})$

205 The DCE contained two value attributes: treatment benefit and risk of common, mild ADR, that were

206 used to compare the rate at which patients were willing to give up a unit change in benefit or harm in

207 exchange for a unit change in another, whilst maintaining the same utility (marginal rates of

208 substitution, MRS). 95% confidence intervals were calculated by Bootstrapping with 1,000

209 replications. Lexicographic preferences were explored by looking for left or right hand bias, using

210 counts of how many respondents continually selected medicine A or B. The influence of psychosocial

211 and sociocognitive factors on preferences for persistence was assessed using exploratory subgroup

212 analyses. Subgroups were selected for analysis if they: (i) had a statistically significant association

213 with adherence (as defined by Morisky or MARS) [22]; and (ii) were confirmed as significant predictors

214 of persistence in other published studies [14]. Log likelihood ratio tests of the base case regression

215 and the models comprising the two subgroups were performed at a 5% level of significance. If the

216 subgroup model was significantly different, the MRS for harms and benefits were calculated for each

217 category within the subgroup.

218

219

## 220 RESULTS

221 The analysis was restricted to nine countries that reached the target sample size. There was an

222 inadequate level of available research support in France and Portugal that resulted in low response

223 (n=11, n=33 respectively) thus these were excluded. Eighty-nine percent (n=2,549) of people who

224 started the survey completed at least one DCE question. These were from Austria (n=321), Belgium

225 (n=175), England (n=315), Germany (n=266), Greece (n=288), Hungary (n=322), Netherlands  
226 (n=231), Poland (n=312) and Wales (n=319).

227

228 Sample characteristics

229 Participants' characteristics are presented in Table 2. Respondents were split almost equally  
230 according to gender (51% male) and employment status (52% employed), had a median age of 60  
231 years, and were prescribed a median of 3 different medicines per day. The majority of patients (54%)  
232 were prescribed medicines that required more than once-daily dosing.

233 Insert Table 2 here

234 Magnitude and statistical significance of attributes

235 Among respondents to the DCE, 91.2% selected the dominant choice while only 2.5% of respondents  
236 showed lexicographic preferences, consistently choosing medicine A (1.77%) or B (0.76%).

237 All four attributes influenced respondents' stated intention to persist with treatment ( $p < 0.01$ ) (Table 3).  
238 Respondents were most likely to persist with the treatment offering greatest benefit ( $\beta = 0.031$ ), least  
239 risk of mild but common ADRs ( $\beta = -0.023$ ), or severe but rare ADRs ( $\beta = 1.553$ ), and the least frequent  
240 dosing regimen ( $\beta = 0.869$ ). The signs and direction of the regression coefficients were consistent with  
241 expectation.

242 Insert Table 3 here

243 All else being equal, the odds of patients stating that they would continue taking their medicines  
244 increased by 3% for every 1 percentage point increase in the chance of treatment benefits, and  
245 increased 2% for every 1 percentage point decrease in the risk of common mild side-effects. A  
246 medicine with the lowest risk of severe ADR (very rare) increased the odds of persistence four-fold,  
247 and the lowest dose frequency (once daily) more than two-fold.

248

249 Comparing preferences

250 Marginal rates of substitution, using treatment benefit as the value attribute, suggest that patients  
251 were willing to forego improvements in treatment benefits in order to: reduce the risk of severe ADR  
252 (forego 50.6 percentage point improvement in treatment benefit for a 'very rare' risk of severe of ADR  
253 as opposed to a rare risk); reduce the frequency of dosing (forego 28.3 percentage point improvement  
254 in treatment benefit for once-daily dosage frequency as opposed to twice daily); and to reduce the risk  
255 of common mild side-effects (forego 7.4 percentage point improvement of treatment benefit for a 10  
256 percentage point reduction in mild ADR) (Table 4). When considering harm as the value attribute,  
257 respondents were also willing to accept an increase in risk of mild ADR to avoid severe ADR (68.6  
258 percentage point increase in risk of mild side-effects for a 'very rare' risk of severe ADR as opposed  
259 to rare); and to move to a less frequent dosing schedule (38.4 percentage point increase in risk of  
260 mild ADR for once daily dose frequency as opposed to twice daily).

261 Insert Table 4 here

262 Exploratory analysis

263 Regressions controlling for psychosocial variables were significantly different from the base-case  
264 regression in 10/12 cases (Appendix 2), but in each case, all four attributes were significant and in the  
265 expected directions.

266

267 Respondents' willingness to trade treatment benefit for once daily dosing, as opposed to twice daily,  
268 was significantly higher for respondents who were unlikely to take their medicines regularly. These  
269 respondents, who had low intentions, were willing to forego an additional 29.9 percentage point benefit  
270 to take medication once, rather than twice a day (i.e. Appendix 2; MRS of lower intentions 49.97  
271 minus MRS of high intentions 20.06). Individuals with high concerns about medicines were also  
272 willing to forego an additional benefit to take medication once, rather than twice a day (22.2 percentage  
273 points); as where those who lacked confidence in their medicines-taking i.e. those with low self-  
274 efficacy (16.6 percentage points) and, those with higher illness concern (willing to forego a 15.5  
275 percentage point improvement in benefit to take medication once, rather than twice a day).

276

277 Respondents' willingness to trade treatment benefit for the lowest risk of ADR (very rare) opposed to  
278 a rare risk was significantly higher for respondents who were (i) unlikely to take their medicines  
279 regularly (people with low intention were willing to forgo a 32.4 percentage point additional benefit for  
280 a very rare risk of severe ADR, than those categorised as high TPB intentions); (ii) demonstrated high  
281 illness concern (24.5 percentage points); and (iii) had high concerns about medicines (23.8  
282 percentage points).

283

284

## 285 DISCUSSION

286 The results of the study suggest that, in addition to treatment benefits, patients place a high value on  
287 reduced risk of severe (but relatively rare) ADRs and less frequent dosing when stating that they  
288 choose to continue taking a medicine. Stated preference to persist is therefore associated with the  
289 willingness to trade potential benefits for reduced harm and increased convenience. The total utility  
290 produced by different combinations of these attributes may have value in assessing patients'  
291 likelihood of persisting with medicines, in the context of health care provider-patient communications,  
292 and the personalisation of medicines, or formulations thereof, to maximise persistence.

293

294 This study has shown that the evidence-based medicine model of health maximisation via use of  
295 treatments with the highest expected net benefit may not necessarily result in the best outcome for  
296 patients if there is misalignment in preferences. Persistence with medications can be considered as  
297 an outcome of a decision patients make about whether the continued taking the medication will  
298 increase their utility [6]. Maximising utility may therefore increase persistence, which may lead to  
299 better health outcomes – even when using a less effective treatment. Our analysis therefore  
300 suggests a mechanism via which the prescribing of alternative treatments might improve persistence  
301 and hence health outcome. We have also found that patients' trade-offs between benefits, harm and  
302 convenience are influenced by psychosocial and sociocognitive factors. Interventions to improve  
303 persistence, grounded in theory and targeted towards psychosocial variables (e.g. barriers to  
304 medicines, self-efficacy / confidence in medicines taking) may therefore improve the probability of

305 persistence directly [22], and indirectly through changing patients' preferences for medicines-related  
306 attributes. This study illustrates the potential for improvements in sociocognitive factors to increase  
307 the utility of routinely prescribed drugs and thus encourage persistence. Further research is  
308 necessary to design and provide evidence on the efficacy of potential interventions. Our findings  
309 suggest that several factors influence persistence, however a simple intervention, such as a guided  
310 conversation or a medicines review, could enable health care professionals to identify barriers to  
311 medicines taking and assess how other people influence perceptions of medicines (subjective norms),  
312 in order increase an individual's self-efficacy via education or counselling.

313

314 Previous DCEs of preferences for medicines reveal that patients are willing to trade benefit for  
315 reduced harm [9,10]. In the context of adherence, a DCE by Mohamed et al. [13] showed that lower  
316 frequency of administration, shorter administration times, and milder ADR appear to improve stated  
317 adherence to antibiotic treatment of CF lung infections. A study of patients with HIV, using a modified  
318 adaptive conjoint analysis, identified pill burden, dosing frequency, and adverse events as having the  
319 greatest impact on patients' perceived ability to adhere to antiretroviral medication regimens [33].

320

321 To our knowledge this is the first study of preferences for persistence with medication to survey a  
322 large multi-national sample; and, the first study to measure both stated preferences and a wide range  
323 of psychosocial factors concurrently. The DCE was generic, based on previously tested actionable  
324 attributes and used European Medicines Agency data and terminology where possible to enable  
325 general application. The selection of psychosocial and sociocognitive factors tested alongside the  
326 DCE attributes was guided by theory and based on empirical evidence.

327

328 There were a number of limitations. Firstly, patients self-selected to participate in the study and we  
329 must therefore acknowledge the risk of selection bias which may influence the results insofar as only  
330 people who were actively interested in expressing their views on their medicines taking behaviour  
331 participated, which may reduce the external validity of our findings. Secondly, our study was  
332 restricted to four attributes to cover benefits, harms and convenience; findings from other studies of

333 preferences for medications (not persistence with) suggest that attributes such as route of  
334 administration [34], quality of life, location / provider, duration of treatment, among others, may also  
335 have a significant influence on preference. The risk attributes were also presented as probabilities  
336 with no indication of frequency or time horizon. It is acknowledged, however, that trading multiple  
337 attributes is cognitively challenging [35]. We aimed to minimise this by piloting the DCE extensively  
338 and by using two methods of displaying risk. Event frequencies were supplemented by pictograms  
339 which were intended to aid interpretation by depicting probabilities graphically and colour-coding  
340 positive and negative effects. Respondents find it much easier to understand pictorial representations  
341 than presenting probabilities in the form of 1 in X chance [36]. Thirdly, the respondents were  
342 diagnosed with hypertension whereas the DCE was aimed to cover a broad spectrum of  
343 pharmaceuticals.. The DCE was not amenable to treatments for hypertension as they are mainly  
344 once daily. Fourthly, the length of the survey (135 items) represents a further limitation, but  
345 completion rates were high as the DCE was purposely put towards the beginning of the survey before  
346 participants were asked to complete any items that may have conditioned their choice [22]. Finally, as  
347 with any stated preference study, the findings need to be confirmed by studies of revealed preference.

348

349 Patients were willing to trade potential benefits, harms, and convenience in responding that they  
350 would persist with treatment. Potentially alterable, psychosocial factors influence the extent of the  
351 trade-offs between these attributes. Persistence may therefore be enhanced directly, through  
352 selection of medicines meeting preferred levels of attributes; or, indirectly through targeting modifiable  
353 psychosocial factors that affect trade-off choices. The novel finding of an interaction between  
354 patients' stated preferences to persist with medication and their sociocognitive characteristics (i.e.  
355 high/low illness concerns, high/low self-efficacy etc.) provides a basis for synergistically effective  
356 approaches aimed to change behaviour (e.g. to increase self-efficacy) and treatment selection (e.g.  
357 reduced dose frequency).

358

359 Acknowledgements: The authors wish to acknowledge Dr Catrin Plumpton (Bangor University); and  
360 the Ascertaining Barriers to Compliance (ABC) Project Team for their participation in internal  
361 meetings, discussing the progress and findings of this research; and, for their internal review of the  
362 report to funders. The funder had no role in the study design; in the collection, analysis, and  
363 interpretation of data; in the writing of the report; and in the decision to submit the paper for  
364 publication.

365 Declaration: The authors declare no conflicts of interest and confirm to have read the Journal's  
366 position on issues involved in ethical publishing and affirm that this report is consistent with those  
367 guidelines. All authors have completed the Unified Competing Interest form at  
368 [www.icmje.org/coi\\_disclosure.pdf](http://www.icmje.org/coi_disclosure.pdf) (available on request from the corresponding author) and declare:  
369 support from the European Union's Seventh Framework Programme [FP7/2007-2013 under grant  
370 agreement n° 223477] for the submitted work; no financial relationships with any organisations that  
371 might have an interest in the submitted work in the previous 3 years; no other relationships or  
372 activities that could appear to have influenced the submitted work.

373 Contributions: All authors contributed substantially to the conception and design of the work; and, to  
374 the acquisition, analysis, or interpretation of data. EAFH drafted the paper and DH and VM revised it  
375 critically for important intellectual content, and gave their final approval of the version to be published.  
376 All authors agree to be accountable for all aspects of the work in ensuring that questions related to  
377 the accuracy or integrity of any part of the work are appropriately investigated and resolved.

378

379



380 References

- 381 1. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppert T, Dobbels F, Fargher  
382 E, Morrison V, Lewek P, Matyjaszczyk M, Mshelia C, Clyne W, Aronson JK, Urquhart J; ABC  
383 Project Team. A new taxonomy for describing and defining adherence to medications. *Br J Clin*  
384 *Pharmacol* 2012; 73: 691-705.
- 385 2. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed  
386 antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories.  
387 *BMJ* 2008; 336: 1114-7.
- 388 3. Osterberg L, Blaschke T. Adherence to Medicines. *NEJM* 2005; 353: 487-97.
- 389 4. Sabaté E. Adherence to Long-Term Therapies: Evidence for Action, World Health Organization,  
390 Geneva, Switzerland, 2003.
- 391 5. Elliott RA, Shinogle JA, Peele P, Bhosle M, Hughes DA. Understanding medication non-  
392 compliance from an economics perspective. *Value in Health* 2008; 11: 600-10.
- 393 6. Lamiraud K, Geoffard P. Therapeutic non-adherence: a rational behavior revealing patient  
394 preferences? *Health Economics* 2007; 16: 1185-204.
- 395 7. Ryan M, Gerard K, Amaya-Amaya M. Using Discrete Choice Experiments to Value Health and  
396 Health Care. The Netherlands: Springer, 2008.
- 397 8. Lancaster K. A new approach to consumer theory. *J Political Economy* 1974; 74: 132-57.
- 398 9. de Bekker-Grob EW, Ryan M, Gerard K. Health Discrete choice experiments in health economics:  
399 a review of the literature. *Health Economics* 2012; 21: 145-72.
- 400 10. Clark MD, Determann D, Petrou S, Moro D, de Bekker-Grob EW. Discrete choice experiments in  
401 health economics: a review of the literature. *Pharmacoeconomics* 2014; 32: 883-902.
- 402 11. Hauber AB, Mohamed AF, Johnson FR, Falvey H. Treatment preferences and medication  
403 adherence of people with Type 2 diabetes using oral glucose-lowering agents. *Diabet Med* 2009;  
404 26: 416-24.
- 405 12. Johnson FR, Ozdemir S, Manjunath R, Hauber AB, Burch SP, Thompson TR. Factors that affect  
406 adherence to bipolar disorder treatments: a stated-preference approach. *Medical Care* 2007; 45:  
407 545-52.

- 408 13. Mohamed AF, Johnson FR, Balp MM, Calado F. Preferences and Stated Adherence for Antibiotic  
409 Treatment of Cystic Fibrosis Pseudomonas Infections. *Patient* 2015; DOI: 10.1007/s40271-015-  
410 0124-1.
- 411 14. Holmes EAF, Hughes DA, Morrison VL. Predicting adherence to medications using health  
412 psychology theories: a systematic review of 20 years of empirical research. *Value in Health*  
413 2014; 17: 863-76.
- 414 15. Turner AP, Kivlahan DR, Sloan AP, Haselkorn JK. Predicting ongoing adherence to disease  
415 modifying therapies in multiple sclerosis: Utility of the health beliefs model. *Mult Scler* 2007; 13:  
416 1146-52.
- 417 16. Apter AJ, Boston RC, George M, Norfleet AL, Tenhave T, Coyne JC, Birck K, Reisine ST,  
418 Cucchiara AJ, Feldman HI. Modifiable barriers to adherence to inhaled steroids among adults with  
419 asthma: It's not just black and white. *J Allergy Clin Immunol* 2003; 111: 1219-26.
- 420 17. Abraham C, Clift S, Grabowski P. Cognitive predictors of adherence to malaria prophylaxis  
421 regimens on return from a malarious region: A prospective study. *Soc Sci Med* 1999; 48: 1641-54.
- 422 18. Rosenstock IM. The health belief model and preventative health behaviour. *Health Education*  
423 *Monographs* 1974; 2: 354-86.
- 424 19. Becker MH. The health belief model and personal health behaviour. *Health Education*  
425 *Monographs* 1974; 2: 324-508.
- 426 20. Ajzen I. The theory of planned behaviour. *Organisational Behaviour and Human Decision*  
427 *Processes* 1991; 50: 179-211.
- 428 21. Leventhal H, Diefenbach M, Leventhal EA. Illness cognition: Using common sense to understand  
429 treatment adherence and affect cognition interactions. *Cognitive Therapy and Research* 1992; 16:  
430 143-63.
- 431 22. Morrison V, Holmes EAF, Parveen S, Plumpton C, Clyne W, De Geest S, Dobbels F, Vrijens B,  
432 Kardas P, Hughes D. Patient-Reported Outcomes Predictors of Self-Reported Adherence to  
433 Antihypertensive Medicines: A Multinational, Cross-Sectional Survey. *Value Health* 2015; 18:  
434 206-16.
- 435 23. Hahn GJ, Shapiro SS. A Catalogue and Computer Programme for the Design and Analysis of  
436 Orthogonal Symmetric and Asymmetric Fractional Factorial Experiments. Report 66-C-165, May  
437 1996.

- 438 24. Street D, Burgess L. The Construction of Optimal Stated Choice Experiments: Theory and  
439 Methods. London: Wiley, 2001.
- 440 25. Broadbent E, Petrie KJ, Main J, Weinman J. The brief illness perception questionnaire. J  
441 Psychosom Res 2006; 60: 631-7.
- 442 26. Horne R. BMQ-S11-Plural. University of Brighton; 1996.
- 443 27. Dobbels F, Moons P, Abraham I, Larsen CP, Dupont L, De Geest S. Measuring symptom  
444 experience of side-effects of immunosuppressive drugs: The Transplant Symptom  
445 Occurrence and symptom distress scale (MTSOSD-59R). *Transpl Int* 2008; 21: 764-73.
- 446 28. Schmid-Mohler G, Thut MP, Wüthrich RP, Denhaerynck K, De Geest S. Non-adherence to  
447 immunosuppressive medication in renal transplant recipients within the scope of the integrative  
448 model of behavioural prediction: a cross-sectional study. *Clin Transplant* 2009; 24: 213-22.
- 449 29. Conner M, Norman P. Predicting Health Behaviour. Open University Press; 1996.
- 450 30. Farmer A, Kinmonth AL, Sutton S. Measuring beliefs about taking hypoglycaemic medication  
451 among people with Type 2 diabetes. *Diabet Med* 2006; 23: 265-70.
- 452 31. Morisky DE, Ang A, Krousel-Wood M, Ward H. Predictive validity of a medication adherence  
453 measure for hypertension control. *J Clin Hypertens* 2008; 10: 348-54.
- 454 32. Horne R. Medication Adherence Report Scale-5. University of Brighton, 1999.
- 455 33. Stone VE, Jordan J, Tolson J, Miller R, Pilon T. Perspectives on adherence and simplicity for HIV-  
456 infected patients on antiretroviral therapy: self-report of the relative importance of multiple  
457 attributes of highly active antiretroviral therapy (HAART) regimens in predicting adherence. *J*  
458 *Acquir Immune Defic Syndr.* 2004; 36: 808-16.
- 459 34. Levitan B, Markowitz M, Mohamed AF, Johnson FR, Alphas L, Citrome L, Bridges JF. Patients'  
460 Preferences Related to Benefits, Risks, and Formulations of Schizophrenia Treatment. *Psychiatr*  
461 *Serv.* 2015; DOI: 10.1176/appi.ps.201400188.
- 462 35. Gigerenzwe G. Reckoning with risk: learning to live with uncertainty. London: Penguin Books,  
463 2002.
- 464 36. Gigerenzer G, Hoffrage U. How to improve Bayesian reasoning without instructions: frequency  
465 formats. *Psychol Rev* 1995; 98: 506-28.

467 **Figures and Tables**

468 Figure 1 Example of a pair wise choice question

469 Table 1. Attribute names and descriptions

470 Table 2. Participant characteristics

471 Table 3. Random effects logit model

472 Table 4. Patients' marginal rates of substitution between treatment benefit, or reduction in  
473 common mild side effects, and other attributes.

474 **Electronic Supplementary Material**

475

476 Appendix 1. Psychosocial measures

477

478 Appendix 2. Results of exploratory subgroup analysis of willingness to trade benefit or mild ADR  
479 with other attributes.





480

481 **Figure 1.** Example of pairwise choice

482

483 We would like you to imagine that you have been prescribed a **new** medicine that you should  
 484 continue taking until your doctor advises otherwise. In the following questions the characteristics of  
 485 two alternative medicines will be described to you, please indicate which medicine you would be  
 486 most likely to continue taking, 'Medicine A or Medicine B'.

487

|  | Medicine A   | Medicine B   |
|--|--|--|
| Mild side-effects<br><i>e.g. feeling sick, diarrhoea</i> | 5 in 10<br> | 1 in 10<br> |
| Number of times you need to take the medicine            | Once a day   | Twice a day  |
| Treatment benefits                                       | 4 in 20<br> | 1 in 20<br> |
| Potentially life-threatening side-effects                | Uncommon: 1 person in 100  | Very Rare: 1 person in 10,000  |

Which medicine would you be most likely to continue taking?



488

489

490 **Table 1.** Attributes and Levels

| Attribute name | Attribute description                          | Level description  | Rationale for levels  |
|----------------|--|--|---|
| Benefit        | Treatment benefits                             | 1 in 20<br>2 in 20<br>4 in 20                                    | Based on typical Numbers Needed to Treat for treatment for chronic conditions (e.g. hypertension, diabetes, ulcerative colitis) |
| Dose           | Number of times you need to take the medicine  | Once a day<br>Twice a day<br>Four times a day                    | The majority of chronic disease treatments are in the range of once to four times daily dosing                                  |
| Mild ADR       | Mild side-effects e.g. feeling sick, diarrhoea | 1 in 10<br>3 in 10<br>5 in 10                                    | Gastrointestinal irritation is a common ADR for many treatments. Frequency based on representative range                        |
| Severe ADR     | Potentially life-threatening side-effects      | Very rare: 1 in 10,000<br>Rare: 1 in 1,000<br>Uncommon: 1 in 100 | Likelihood of life-threatening ADRs are typically uncommon to very rare   |

491

492

493 **Table 2.** Values of regression variables used to estimate utility and probability of persistence with 5-  
 494 ASAs for ulcerative colitis

|  | Drug name        |            |             |             | References |
|--|------------------|------------|-------------|-------------|------------|
|  | sulfasalazine    | mesalamine | olsalazine  | balsalazide |            |
| Probability of remission                   | 0.37             | 0.42       | 0.33        | 0.24        | [35]       |
| Probability of ADR                         | 0.34             | 0.13       | 0.20        | 0.10        | [35]       |
| Frequency of severe ADR (aplastic anaemia) | Very rare        | Rare       | Very rare   | Very rare   | SmPC       |
| Maintenance dose frequency                 | Four times daily | Once a day | Twice a day | Twice a day | SmPC       |

495

496 SmPC summary of product characteristics

497

498 **Table 3.** Random effects logit model

| Attribute                                    | Coefficient (95%CI)     | p-value | Odds Ratio |
|--|-------------------------|---------|------------|
| Severe ADR - Very rare                       | 1.553 (1.469, 1.637)    |         | 4.726      |
| Severe ADR - Rare                            | -0.444 (-0.488, -0.401) | 0.0000  | 0.641      |
| Severe ADR - Uncommon                        | -1.109 (-1.149, -1.068) | 0.0000  | 0.330      |
| Dose - Once a day                            | 0.869 (0.776, 0.961)    |         | 2.383      |
| Dose - Twice a day                           | -0.296 (-0.341, -0.250) | 0.0000  | 0.744      |
| Dose - Four times a day                      | -0.573 (-0.620, -0.526) | 0.0000  | 0.564      |
| Treatment benefit                            | 0.031 (0.028, 0.034)    | 0.0000  | 1.031      |
| Common mild side-effects                     | -0.023 (-0.024, -0.022) | 0.0000  | 0.978      |
| Constant                                     | 0.452 (0.414, 0.490)    | 0.0000  | 1.572      |
| Number of observations                       | 22277                   |         |            |
| Number of groups                             | 2549                    |         |            |
| Wald chi <sup>2</sup> (6 degrees of freedom) | 1465                    |         |            |
| Log likelihood                               | -11952.52               |         |            |

499

500

501



502 **Table 4.** Patients' marginal rates of substitution between treatment benefit or reduction in common  
 503 mild side-effects and other attributes

| Attribute                | Marginal rate of substitution (MRS) |                                 |
|--------------------------|-------------------------------------|---------------------------------|
|                          | Treatment benefit<br>% (95% CI)     | Risk of mild ADRs<br>% (95% CI) |
| Severe ADR - Very rare   | 50.58 (46.07, 57.87)                | -68.60 (-72.35, -63.98)         |
| Severe ADR - Rare        | -14.48 (-16.99, -12.77)             | 19.64 (17.49, 21.60)            |
| Severe ADR - Uncommon    | -36.10 (-41.24, -32.94)             | 48.96 (45.90, 51.25)            |
| Dose - Once a day        | 28.29 (25.18, 33.11)                | -38.36 (-42.50, -34.77)         |
| Dose - Twice a day       | -9.63 (-11.88, -8.14)               | 13.05 (11.15, 15.33)            |
| Dose - Four times a day  | -18.66 (-21.51, -16.67)             | 25.31 (22.95, 27.60)            |
| Treatment benefit        |                                     | -1.36 (-1.49, -1.17)            |
| Common mild side-effects | -0.74 (-0.85, -0.67)                |                                 |

504

505

## Appendix 1: Psychosocial measures

| Psychological theory, model, variable           | Number of items {score} | Item description  | Scoring scale  |
|---|-------------------------|---|--|
| <b>Sociocognitive theory:</b>                   |                         |   |  |
| Theory of Planned Behaviour                     |                         |   |  |
| Subjective norms                                | 3-items {3-15}          | <ol style="list-style-type: none"> <li>1. My doctor or nurse would approve of me taking my medicines regularly</li> <li>2. My wife/husband/partner would approve of me taking my medicines regularly</li> <li>3. Members of my family or close relatives would approve of me taking my medicines regularly</li> </ol>   | 5-point Likert scale:<br>I agree a lot {5}<br>I agree a little<br>I neither agree or disagree<br>I disagree a little<br>I disagree a lot {1} |
| Barriers  | 1-items {3-15}          | <ol style="list-style-type: none"> <li>1. Changes to my daily routine would make it more difficult for me to take my medicines regularly</li> </ol>   |  |
| Intention                                       | 2-items {2-10}          | <ol style="list-style-type: none"> <li>1. It is likely that I will take my medicines regularly</li> <li>2. I intend to take my medicines regularly</li> </ol>   |  |
| Self-efficacy                                   | 2-items {2-10}          | <ol style="list-style-type: none"> <li>1. Overall, how confident are you that you will always take your medications as prescribed?</li> <li>2. Overall, how confident are you that you will always take your medications at the prescribed times?</li> </ol>  | 5-point Likert scale:<br>Not at all confident {1}<br>Somewhat confident<br>Very confident<br>Extremely confident<br>Completely confident {5} |
| BRIGHT Environmental Constraints / Facilitators |                         |   |  |
| Social support                                  | 7-items {0-35}          | <ol style="list-style-type: none"> <li>1. Was there someone who reminded you to take your medicines?</li> <li>2. Was there someone who helped you to prepare the medicines?</li> <li>3. Was there someone who encouraged you to take your medicines correctly?</li> <li>4. Was there someone who gave practical tips to make it easier for you to take your medicines?</li> <li>5. Was there someone who adapted his or her own life habits (waking up, schedule...) to make it easier for you to take your medicines?</li> </ol> | 5-point Likert scale:<br>In the past 4 weeks ...<br>Never {0}<br>Occasionally<br>Sometimes<br>Frequently<br>All the time {4}                 |

| Psychological theory, model, variable   | Number of items {score} | Item description   | Scoring scale   |
|---|-------------------------|--|---|
|   |                         | 6. Was there someone who understood the problems or discomfort that resulted from your medicines?<br>7. Was there someone who reprimanded you because you didn't take your medicines correctly?  |   |
| BRIGHT Barriers   | 15-items {0-75}         | 1. I ran out of medicines<br>2. I was confused about which medicines to take<br>3. I did not want other people to know that I have a health problem<br>4. Something disrupted my daily medicine routine (e.g., I was on holiday)<br>5. I was forgetful<br>6. I could not afford to buy my medicines<br>7. I felt depressed or overwhelmed<br>8. I forgot to take my medicines with me when leaving the house<br>9. I had too many medicines to take<br>10. I suffered from the side effects of my medicine.<br>11. I had to take too many different doses during the day<br>12. I had problems swallowing the large pills of my medicines<br>13. I did not like the taste of my medicines<br>14. I had problems removing the medicines from the package<br>15. I had problems drinking enough water to swallow the medicines | 5-point Likert scale:<br>In the past year ...<br>Never {0}<br>Occasionally<br>Sometimes<br>Frequently<br>All the time {4} |
| <b>Self-regulation theory:</b><br>Illness Representations<br>Illness consequences | 1-item {0-10}           | 1. How much does your illness affect your life?  | {0} - no affect at all<br>{1 2 3 4 5 6 7 8 9}<br>{10} - severely affects my life  |
| Personal control  | 1-item {0-10}           | 1. How much control do you feel you have over your illness?  | {0} - absolutely no control<br>{1 2 3 4 5 6 7 8 9}<br>{10} - extreme amount of control                                    |

| <b>Psychological theory, model, variable</b> | <b>Number of items {score}</b> | <b>Item description</b>   | <b>Scoring scale</b>   |
|--|--------------------------------|---|--|
| Treatment control                            | 1-item<br>{0-10}               | 1. How much do you think your treatment can help your illness?  | {0} - not at all<br>{1 2 3 4 5 6 7 8 9}<br>{10} - extremely helpful                                    |
| Illness concern                              | 1-item<br>{0-10}               | 1. How concerned are you about your illness?  | {0} - not at all concerned<br>{1 2 3 4 5 6 7 8 9}<br>{10} - extremely concerned                        |
| Treatment Beliefs                            |                                |   |  |
| Necessity of medicine                        | 5-items<br>{5-25}              | <ol style="list-style-type: none"> <li>1. My health, at present, depends on these medicines</li> <li>2. My life would be impossible without these medicines</li> <li>3. Without these medicines I would be very ill</li> <li>4. My health in the future will depend on these medicines</li> <li>5. These medicines protect me from becoming worse</li> </ol>  | 5-point Likert scale:<br>Strongly Agree {5}<br>Agree<br>Uncertain<br>Disagree<br>Strongly Disagree {1} |
| Concerns about medicine                      | 6-items<br>{6-30}              | <ol style="list-style-type: none"> <li>1. Having to take these medicines worries me</li> <li>2. I sometimes worry about long-term effects of these medicines</li> <li>3. These medicines are a mystery to me</li> <li>4. These medicines disrupt my life</li> <li>5. I sometimes worry about becoming too dependent on these medicines</li> <li>6. These medicines give me unpleasant side effects</li> </ol> | 5-point Likert scale:<br>Strongly Agree {5}<br>Agree<br>Uncertain<br>Disagree<br>Strongly Disagree {1} |

**Appendix 2.** Results of exploratory subgroup analysis of willingness to trade benefit or mild ADR with other attributes, presented by psychological theory, model, and factor

| Psychological theory<br>Model<br>Factor   | Trade-off                | Subgroup<br>MRS (95% confidence interval) |                           |
|---|--------------------------|---|---------------------------|
| <b>Sociocognitive Theory</b>  |                          |   |                           |
| <b>Theory of Planned Behaviour</b>  |                          |   |                           |
| Subjective norms: <i>Perception that persistence is influenced by approval of others: doctor, nurse, partner, family.</i> |                          | Higher influence of others                | Lower influence of others |
| Mild ADR / Benefit  | -0.64 (-0.79, -0.56)     | -0.77 (-0.94, -0.68)                      |                           |
| Once daily dose / Benefit   | 23.25 (19.23, 29.40)     | 31.77 (27.06, 39.57)                      |                           |
| Twice daily dose / Benefit  | -8.39 (-11.58, -6.60)    | -9.70 (-13.27, -7.77)                     |                           |
| Four times a day dose / Benefit   | -14.86* (-18.26, -12.22) | -22.07* (-26.78, -19.04)                  |                           |
| Very rare severe ADR / Benefit  | 50.91 (43.99, 60.89)     | 45.56 (39.24, 54.81)                      |                           |
| Rare severe ADR / Benefit   | -14.85 (-18.34, -12.39)  | -12.23 (-15.39, -9.77)                    |                           |
| Uncommon severe ADR / Benefit   | -36.06 (-43.10, -31.43)  | -33.33 (-39.89, -29.10)                   |                           |
| Benefit / Mild ADR  | -1.55 (-1.80, -1.27)     | -1.29 (-1.48, -1.06)                      |                           |
| Once daily dose / Mild ADR  | -36.14 (-42.92, -30.20)  | -41.01 (-47.13, -35.56)                   |                           |
| Twice daily dose / Mild ADR   | 13.04 (10.11, 16.67)     | 12.52 (10.00, 15.72)                      |                           |
| Four times a day dose / Mild ADR  | 23.10 (19.24, 26.99)     | 28.49 (24.98, 32.02)                      |                           |
| Very rare severe ADR / Mild ADR   | -79.14* (-86.43, -71.82) | -58.81* (-64.10, -53.07)                  |                           |
| Rare severe ADR / Mild ADR  | 23.08* (19.59, 26.38)    | 15.78* (12.99, 18.62)                     |                           |
| Uncommon severe ADR / Mild ADR  | 56.06* (50.93, 60.76)    | 43.03* (39.34, 46.50)                     |                           |
| Barriers: <i>Changes to daily routine would make it more difficult to take medicines regularly</i>                        |                          | Higher barriers                           | Lower barriers            |
| Mild ADR / Benefit  | -0.77 (-0.92, -0.67)     | -0.59 (-0.74, -0.52)                      |                           |
| Once daily dose / Benefit   | 30.33 (25.80, 36.85)     | 22.68 (18.57, 28.91)                      |                           |
| Twice daily dose / Benefit  | -9.49 (-12.40, -7.46)    | -8.24 (-11.43, -6.24)                     |                           |
| Four times a day dose / Benefit   | -20.84* (-24.68, -17.97) | -14.44* (-17.94, -11.98)                  |                           |
| Very rare severe ADR / Benefit  | 46.27 (40.24, 55.68)     | 49.72 (43.71, 59.66)                      |                           |
| Rare severe ADR / Benefit   | -12.73 (-16.20, -10.49)  | -14.27 (-18.07, -11.86)                   |                           |
| Uncommon severe ADR / Benefit   | -33.53 (-39.42, -29.24)  | -35.45 (-42.26, -31.38)                   |                           |
| Benefit / Mild ADR  | -1.30* (-1.49, -1.09)    | -1.69* (-1.93, 1.36)                      |                           |
| Once daily dose / Mild ADR  | -39.43 (-44.74, -34.36)  | -38.23 (-45.75, -31.34)                   |                           |
| Twice daily dose / Mild ADR   | 12.34 (9.84, 15.07)      | 13.89 (10.28, 18.00)                      |                           |
| Four times a day dose / Mild ADR  | 27.09 (23.74, 30.44)     | 24.35 (19.98, 29.05)                      |                           |
| Very rare severe ADR / Mild ADR   | -60.15 (-64.87, -55.26)  | -83.81* (-91.51, -75.28)                  |                           |
| Rare severe ADR / Mild ADR  | 16.55 (14.18, 19.01)     | 24.06* (20.23, 27.60)                     |                           |
| Uncommon severe ADR / Mild ADR  | 43.59 (40.27, 46.51)     | 59.75* (54.13, 64.69)                     |                           |
| Intention: <i>Likely to and/or intend to take medicines</i>   |                          | Higher intentions                         | Lower intentions          |
| Mild ADR / Benefit  | -0.58* (-0.67, -0.52)    | -1.10* (-1.58, -0.86)                     |                           |
| Once daily dose / Benefit   | 20.06* (17.08, 24.18)    | 49.97* (38.10, 70.71)                     |                           |
| Twice daily dose / Benefit  | -6.67* (-8.77, -5.28)    | -16.64* (-24.72, -11.80)                  |                           |
| Four times a day dose / Benefit   | -13.39* (-15.72, -11.58) | -33.34* (-46.34, -25.70)                  |                           |
| Very rare severe ADR / Benefit  | 40.26* (36.21, 45.97)    | 72.70* (56.78, 101.43)                    |                           |
| Rare severe ADR / Benefit   | -11.10* (-13.20, -9.48)  | -21.31* (-31.12, -16.06)                  |                           |
| Uncommon severe ADR / Benefit   | -29.16* (-33.11, -26.36) | -51.39* (-71.54, -40.64)                  |                           |
| Benefit / Mild ADR  | -1.73* (-1.91, -1.50)    | -0.91* (-1.16, -0.64)                     |                           |
| Once daily dose / Mild ADR  | -34.64 (-40.38, -29.79)  | -45.36 (-52.58, -38.07)                   |                           |
| Twice daily dose / Mild ADR   | 11.51 (9.09, 14.70)      | 15.10 (11.37, 18.86)                      |                           |
| Four times a day dose / Mild ADR  | 23.12 (20.00, 26.34)     | 30.26 (25.79, 34.79)                      |                           |
| Very rare severe ADR / Mild ADR   | -69.53 (-74.41, -63.71)  | -65.99 (-73.01, -59.12)                   |                           |
| Rare severe ADR / Mild ADR  | 19.17 (16.56, 21.79)     | 19.34 (16.13, 22.86)                      |                           |
| Uncommon severe ADR / Mild ADR  | 50.36 (46.44, 53.33)     | 46.65 (42.12, 50.80)                      |                           |

| Self-efficacy: <i>Confidence of taking medicines and/or at the prescribed times</i> | Higher confidence        | Lower confidence         |
|---|--------------------------|--------------------------|
| Mild ADR / Benefit  | -0.58* (-0.68, -0.52)    | -0.93* (-1.17, -0.78)    |
| Once daily dose / Benefit   | 21.31* (18.08, 25.71)    | 37.90* (30.67, 48.12)    |
| Twice daily dose / Benefit  | -7.26 (-9.63, -5.80)     | -12.34 (-16.92, -9.20)   |
| Four times a day dose / Benefit   | -14.06* (-16.46, -12.10) | -25.56* (-32.06, -20.90) |
| Very rare severe ADR / Benefit  | 44.11 (39.51, 50.42)     | 55.71 (47.02, 68.98)     |
| Rare severe ADR / Benefit   | -12.25 (-14.64, -10.40)  | -15.90 (-20.92, -12.80)  |
| Uncommon severe ADR / Benefit   | -31.86 (-36.06, -28.76)  | -39.81 (-49.21, -33.43)  |
| Benefit / Mild ADR  | -1.71 (-1.91, -1.47)     | -1.08* (-1.28, -0.86)    |
| Once daily dose / Mild ADR  | -36.50 (-42.82, -31.06)  | -40.92 (-46.81, -35.06)  |
| Twice daily dose / Mild ADR   | 12.43 (10.02, 16.01)     | 13.33 (10.27, 16.46)     |
| Four times a day dose / Mild ADR  | 24.07 (20.54, 27.42)     | 27.59 (23.95, 31.05)     |
| Very rare severe ADR / Mild ADR   | -75.55* (-82.07, -68.88) | -60.14* (-66.36, -54.28) |
| Rare severe ADR / Mild ADR  | 20.99 (18.03, 24.01)     | 17.16 (14.27, 20.21)     |
| Uncommon severe ADR / Mild ADR  | 54.56* (50.02, 58.65)    | 42.98* (39.13, 46.59)    |

### Sociocognitive Theory

#### Bright: Environmental Constraints / Facilitators

| Social support: <i>Support from people in personal environment</i> | Higher social support    | Lower social support     |
|--|--------------------------|--------------------------|
| Mild ADR / Benefit   | -0.64 (0.78, -0.56)      | -0.87 (-1.09, -0.74)     |
| Once daily dose / Benefit  | 25.76 (21.93, 32.10)     | 30.73 (24.84, 39.28)     |
| Twice daily dose / Benefit   | -8.44 (-11.46, -6.69)    | -10.67 (-14.99, -7.87)   |
| Four times a day dose / Benefit                                    | -17.32 (-21.13, -14.65)  | -20.06 (-25.21, -16.61)  |
| Very rare severe ADR / Benefit                                     | 42.01* (36.55, 50.80)    | 61.01* (51.62, 75.39)    |
| Rare severe ADR / Benefit  | -11.52 (-14.65, -9.44)   | -17.24 (-22.12, -14.04)  |
| Uncommon severe ADR / Benefit                                      | -30.49* (-36.48, -26.85) | -43.76* (-53.90, -37.17) |
| Benefit / Mild ADR   | -1.55* (-1.78, -1.29)    | -1.15 (-1.36, -0.92)     |
| Once daily dose / Mild ADR   | -40.02 (-46.49, -34.07)  | -35.39 (-41.63, -29.68)  |
| Twice daily dose / Mild ADR  | 13.11 (10.32, 16.79)     | 12.29 (9.40, 15.65)      |
| Four times a day dose / Mild ADR                                   | 26.91 (23.10, 30.77)     | 23.10 (19.43, 26.43)     |
| Very rare severe ADR / Mild ADR                                    | -65.25 (-71.52, -58.83)  | -70.25 (-76.67, -63.43)  |
| Rare severe ADR / Mild ADR   | 17.90 (14.93, 21.19)     | 19.86 (16.75, 23.03)     |
| Uncommon severe ADR / Mild ADR                                     | 47.36 (43.06, 51.18)     | 50.40 (45.86, 54.30)     |

### Self-regulation Theory

#### Illness Representations

| Illness consequences: <i>How much does your illness affect your life?</i> | Higher illness consequences | Lower illness consequences |
|---|-----------------------------|----------------------------|
| Mild ADR / Benefit  | -0.77 (-0.94, -0.65)        | -0.64 (-0.76, -0.57)       |
| Once daily dose / Benefit   | 32.67 (27.43, 40.65)        | 22.58 (18.88, 28.03)       |
| Twice daily dose / Benefit  | -10.18 (-13.80, -7.87)      | -8.07 (-10.83, -6.17)      |
| Four times a day dose / Benefit   | -22.50* (-27.20, -19.10)    | -14.51* (-17.46, -12.22)   |
| Very rare severe ADR / Benefit  | 53.76 (45.87, 64.60)        | 43.36 (38.35, 51.07)       |
| Rare severe ADR / Benefit   | -15.24 (-19.24, -12.56)     | -12.16 (-14.94, -10.17)    |
| Uncommon severe ADR / Benefit   | -38.52 (-46.03, -33.07)     | -31.20 (-36.62, -27.56)    |
| Benefit / Mild ADR  | -1.31* (-1.53, -1.07)       | -1.56 (-1.76, -1.32)       |
| Once daily dose / Mild ADR  | -42.70 (-49.51, -36.83)     | -35.34 (-41.33, -29.57)    |
| Twice daily dose / Mild ADR   | 13.30 (10.37, 16.80)        | 12.63 (9.80, 15.77)        |
| Four times a day dose / Mild ADR  | 29.40 (25.49, 33.59)        | 22.71 (19.28, 25.93)       |
| Very rare severe ADR / Mild ADR   | -70.26 (76.95, -64.03)      | -67.84 (-73.64, -61.77)    |
| Rare severe ADR / Mild ADR  | 19.92 (16.77, 23.28)        | 19.03 (16.27, 22.06)       |
| Uncommon severe ADR / Mild ADR  | 50.34 (45.92, 54.69)        | 48.82 (44.94, 52.40)       |

| Personal control: <i>How much control do you feel you have over your illness?</i> | Higher personal control | Lower personal control |
|---|-------------------------|------------------------|
| Mild ADR / Benefit  | -0.83 (-1.01, -0.71)    | -0.60 (-0.72, -0.53)   |
| Once daily dose / Benefit   | 30.79 (24.97, 38.61)    | 24.53 (20.66, 30.01)   |

|                                  |                          |                          |
|----------------------------------|--------------------------|--------------------------|
| Twice daily dose / Benefit       | -10.26 (-13.77, -7.52)   | -8.25 (-11.03, -6.39)    |
| Four times a day dose / Benefit  | -20.53 (-25.22, -17.20)  | -16.28 (-19.41, -13.96)  |
| Very rare severe ADR / Benefit   | 58.86* (50.95, 71.72)    | 39.59* (34.61, 47.11)    |
| Rare severe ADR / Benefit        | -16.64 (-20.96, -13.42)  | -11.08 (-14.01, -9.20)   |
| Uncommon severe ADR / Benefit    | -42.23* (-51.55, -36.86) | -28.51* (-33.68, -25.19) |
| Benefit / Mild ADR               | -1.21 (-1.41, -0.99)     | -1.67 (-1.89, -1.40)     |
| Once daily dose / Mild ADR       | -37.28 (-43.27, -31.74)  | -40.96 (-47.13, -34.53)  |
| Twice daily dose / Mild ADR      | 12.42 (9.48, 15.49)      | 13.78 (10.76, 17.26)     |
| Four times a day dose / Mild ADR | 24.85 (21.23, 28.23)     | 27.18 (23.19, 30.67)     |
| Very rare severe ADR / Mild ADR  | -71.27 (-77.02, -65.43)  | -66.11 (-72.54, -59.50)  |
| Rare severe ADR / Mild ADR       | 20.14 (17.28, 23.25)     | 18.50 (15.62, 21.65)     |
| Uncommon severe ADR / Mild ADR   | 51.12 (47.16, 54.78)     | 47.61 (43.33, 51.46)     |

Treatment control: *How much do you think your treatment can help your illness?*

Higher treatment control

Lower treatment control

|                                  |                          |                          |
|----------------------------------|--------------------------|--------------------------|
| Mild ADR / Benefit               | -0.67 (-0.80, -0.60)     | -0.77 (-0.96, -0.65)     |
| Once daily dose / Benefit        | 24.35 (20.81, 29.84)     | 32.92 (27.15, 41.82)     |
| Twice daily dose / Benefit       | -8.56 (-11.27, -6.77)    | -10.19 (-14.33, -7.46)   |
| Four times a day dose / Benefit  | -15.79* (-18.89, -13.57) | -22.74* (-28.29, -19.18) |
| Very rare severe ADR / Benefit   | 49.91 (44.64, 58.58)     | 46.26 (39.16, 57.57)     |
| Rare severe ADR / Benefit        | -14.28 (-17.33, -12.30)  | -12.60 (-16.86, -9.92)   |
| Uncommon severe ADR / Benefit    | -35.64 (-41.91, -31.83)  | -33.66 (-41.27, -28.44)  |
| Benefit / Mild ADR               | -1.48 (-1.67, -1.25)     | -1.30 (-1.54, -1.04)     |
| Once daily dose / Mild ADR       | -36.12 (-42.10, -30.87)  | -42.90 (-49.92, -36.54)  |
| Twice daily dose / Mild ADR      | 12.69 (10.16, 15.96)     | 13.27 (10.07, 16.82)     |
| Four times a day dose / Mild ADR | 23.43 (19.95, 26.71)     | 29.63 (25.71, 33.81)     |
| Very rare severe ADR / Mild ADR  | -74.05 (-79.96, -68.30)  | -60.27* (-66.63, -53.91) |
| Rare severe ADR / Mild ADR       | 21.18 (18.46, 24.12)     | 16.41 (13.37, 20.09)     |
| Uncommon severe ADR / Mild ADR   | 52.87 (48.71, 56.44)     | 43.85* (39.62, 47.88)    |

Illness concern: *How concerned are you about your illness?*

Higher illness concern

Lower illness concern

|                                  |                          |                          |
|----------------------------------|--------------------------|--------------------------|
| Mild ADR / Benefit               | -0.90* (-1.10, -0.78)    | -0.51* (-0.61, -0.44)    |
| Once daily dose / Benefit        | 35.45* (29.60, 44.41)    | 19.98* (16.30, 25.06)    |
| Twice daily dose / Benefit       | -11.91 (-16.01, -9.30)   | -6.61 (-9.32, -4.77)     |
| Four times a day dose / Benefit  | -23.54* (-28.63, -20.11) | -13.37* (-16.22, -11.12) |
| Very rare severe ADR / Benefit   | 60.83* (52.54, 73.78)    | 36.33* (31.85, 43.05)    |
| Rare severe ADR / Benefit        | -17.17* (-21.47, -14.36) | -10.07* (-12.86, -8.02)  |
| Uncommon severe ADR / Benefit    | -43.66* (-52.71, -37.86) | -26.26* (-30.82, -23.13) |
| Benefit / Mild ADR               | -1.11* (-1.29, -0.91)    | -1.98* (-2.25, -1.63)    |
| Once daily dose / Mild ADR       | -39.40 (-45.00, -34.82)  | -39.55 (-47.39, -32.48)  |
| Twice daily dose / Mild ADR      | 13.24 (10.82, 16.22)     | 13.09 (9.39, 17.41)      |
| Four times a day dose / Mild ADR | 26.16 (23.07, 29.40)     | 26.47 (21.82, 30.81)     |
| Very rare severe ADR / Mild ADR  | -67.61 (-73.02, -62.02)  | -71.91 (-79.68, -63.11)  |
| Rare severe ADR / Mild ADR       | 19.08 (16.56, 21.61)     | 19.93 (16.15, 23.72)     |
| Uncommon severe ADR / Mild ADR   | 48.52 (44.84, 51.78)     | 51.98 (46.36, 56.85)     |

## Self-regulation Theory

### Treatment Beliefs

Concerns about medicine

Higher concerns about medicines

Lower concerns about medicines

|                                 |                          |                          |
|---------------------------------|--------------------------|--------------------------|
| Mild ADR / Benefit              | -1.01* (-1.33, -0.85)    | -0.53* (-0.63, -0.47)    |
| Once daily dose / Benefit       | 41.48* (33.90, 54.45)    | 19.31* (16.38, 23.61)    |
| Twice daily dose / Benefit      | -13.34* (18.84, -10.10)  | -6.62* (-8.99, -5.13)    |
| Four times a day dose / Benefit | -28.14* (-36.63, -23.24) | -12.70* (-15.11, 10.84)  |
| Very rare severe ADR / Benefit  | 63.88* (52.54, 82.42)    | 40.06* (35.95, 46.87)    |
| Rare severe ADR / Benefit       | -17.70 (-23.79, -13.92)  | -11.31 (-13.94, -9.60)   |
| Uncommon severe ADR / Benefit   | -46.17* (-59.47, -38.47) | -28.75* (-33.10, -25.81) |
| Benefit / Mild ADR              | -0.99* (-1.18, -0.75)    | -1.90* (-2.12, -1.60)    |
| Once daily dose / Mild ADR      | -40.89 (-46.88, -34.80)  | -36.77 (-43.18, -30.91)  |

|                                  |                          |                          |
|----------------------------------|--------------------------|--------------------------|
| Twice daily dose / Mild ADR      | 13.15 (10.18, 16.36)     | 12.60 (9.62, 16.13)      |
| Four times a day dose / Mild ADR | 27.74 (24.20, 31.29)     | 24.17 (20.44, 27.60)     |
| Very rare severe ADR / Mild ADR  | -62.97* (-68.84, -57.12) | -76.27* (-83.20, -69.36) |
| Rare severe ADR / Mild ADR       | 17.45 (14.46, 20.80)     | 21.53 (18.31, 24.93)     |
| Uncommon severe ADR / Mild ADR   | 45.52* (41.84, 48.88)    | 54.74* (49.92, 58.89)    |

---

Notes. MRS. Marginal Rate of Substitution between attributes. \* Indicates statistically significant subgroups ( $p < 0.004$ , critical p-value for multiple comparison for 12 subgroups). Spilt sample analysis not significantly different to base case for: Sociocognitive theory, BRIGHT Barriers: problems with taking medicines or taking them on time  $p = 0.0093$ ; and, Self-regulation Theory, Treatment beliefs: beliefs about the necessity of medicine  $p = 0.0645$ ; therefore marginal rates of substitution were not calculated.