Patient Preference and Adherence

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ORIGINAL RESEARCH

Elicitation of health state utilities associated with the mode of administration of drugs acting on the prostacyclin pathway in pulmonary arterial hypertension

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Introduction: Pulmonary arterial hypertension (PAH) is a rare, incurable disease associated with decreased life expectancy and a marked impact on quality of life (QoL). There are three classes of drugs available for treatment: endothelin receptor antagonists (ERA), drugs acting on nitric oxide pathway (riociguat and phosphodiesterase type 5 inhibitors [PDE5i]), and drugs acting on prostacyclin pathway. The latter have widely different modes of administration – continuous intravenous infusion, continuous subcutaneous infusion, inhaled, and oral – each associated with variable treatment burden, and implications for health economic assessment. This study aimed to establish utility values associated with different modes of administration of drugs acting on the prostacyclin pathway for use in economic evaluations of PAH treatments.

Methods: A UK general public sample completed the EQ-5D-5L and valued four health states in time trade-off interviews. The health states drafted from literature and interviews with PAH experts (n=3) contained identical descriptions of PAH and ERA/PDE5i treatment, but differed in description of administration including oral (tablets), inhaled (nebulizer), continuous subcutaneous infusion, and continuous intravenous infusion.

Results: A total of 150 participants (63% female; mean age 37 years) completed interviews. Utilities are presented as values between 0 and 1, with 0 representing the state of being dead and 1 representing being in full health. The mean (SD) utility for oral health state was 0.85 (0.16), while all other health states were significantly lower at 0.74 (0.27) for inhaled (p=0.001), 0.59 (0.31) for subcutaneous (p<0.001) and 0.54 (0.32) for intravenous (p<0.001), indicating that there are disutilities (negative differences) associated with non-oral health states. Disutilities were –0.11 for inhaled, –0.26 for subcutaneous, and –0.31 for intravenous administration.

Conclusion: The results demonstrate quantifiable QoL differences between modes of administration of drugs acting on the prostacyclin pathway. QoL burden should be considered for economic evaluation of drugs for PAH treatment.

Keywords: pulmonary arterial hypertension, health-related quality of life, prostacyclin pathway, cost-utility, process utility, time trade-off

Introduction

Pulmonary arterial hypertension (PAH) is a rare, chronic and progressive disease characterized by increased pulmonary vascular resistance which ultimately leads to right ventricular failure, profound functional limitations, and death.[1–4] The New York Heart Association (NYHA) and World Health Organization (WHO) define four functional classes (FC) of pulmonary hypertension that are used to classify severity in PAH,

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with Class I representing patients with no limitation of physical activity through to Class IV in which patients are unable to carry out any physical activity without symptoms.[5,6] Median survival in untreated idiopathic disease is less than 3 years[7] and, despite therapeutic advances, mortality remains high.[8]

The pathophysiology of PAH is not yet completely understood. Three key pathogenic pathways have been identified and can be targeted with pharmaceuticals: the endothelin receptor antagonists (ERA) acting on the endothelin pathway, the phosphodiesterase type 5 inhibitors (PDE5i) and a soluble guanylate cyclase stimulator acting on the nitric oxide pathway, and several drugs acting on the prostacyclin (PGI2) pathway.[9] Given the progressive and ultimately terminal nature of PAH, the overall treatment goal is to reduce disease progression and achieve a low risk status (eg, WHO FC I or II and no progression of symptoms).[6] Treatment guidelines recommend that for patients who fail to achieve an adequate clinical response with initial monotherapy, sequential double or triple combination therapy is utilized.[6] Growing evidence points to the benefits of combining different treatments to target multiple pathways simultaneously.[1,10–12]

Epoprostenol, the first therapy for PAH acting on the PGI2 pathway, was approved in the United States in 1995 (and a year later in Europe) for use as a continuous intravenous infusion.[1] Agents acting on the PGI2 pathway are, however, underused in clinical practice,[8,13] being generally reserved for higher risk patients presenting in NYHA/WHO FC IV or with rapidly progressing symptoms.[2] This is primarily on account of their mode of administration, which may be intravenous via a central venous catheter. Furthermore, the practical and personal implications of such treatments, and the subsequent impact on the patients' health-related quality of life (HRQL), should not be overlooked.[14,15] Other treatments acting on this pathway available in Europe include the prostacyclin analogs treprostinil (continuous intravenous or subcutaneous infusion) and iloprost (intravenous or inhaled), and the IP receptor agonist selexipag (oral).[13,15]

Epoprostenol and treprostinil, when administered by continuous intravenous infusion, have been associated with potentially fatal adverse events such as catheter-related sepsis.[8,16–18] While treprostinil can also be administered subcutaneously, this has been associated with intolerable infusion site pain in some patients.[19] Iloprost can be administered as a continuous intravenous infusion or as an inhaled treatment using a nebulizer device. This also comes with some potential difficulties for patients because the nebulizers need to be taken every 2–3 hours, which is time consuming.[20]

Overall, the burden of PGI2 pathway treatments and the systemic side effects may contribute to the reluctance of patients to accept these therapies or make it difficult for patients to adhere to the treatment schedule. To overcome these barriers, oral therapies have been developed.[21,22]

As new treatments become available, it is important to assess their cost-effectiveness in relation to other existing treatments in order to demonstrate their value to health technology assessment bodies, payers, the wider clinical audience, and decision makers.[23–27] This can be done as part of cost-utility analyses (CUAs).[26,27] In a CUA, the quality of life (QoL) component is measured by utilities, which represent strength of preference for a particular health state, and are measured on a scale of 0 to 1, with 0 representing the state of being dead and 1 representing being in full health.[27,28]

In order to incorporate the strength of preference for prostacyclin analogs, it is necessary to use utilities that represent the different modes of administration of these treatments. While utilities exist that take into account the PAH disease burden by FC,[6] there are currently no published utility values relating to the unique mode of administration of PAH drugs. Thus, the aim of this research was to elicit robust utility values associated with four health states corresponding to different modes of oral and non-oral treatment administration of drugs acting on the prostacyclin pathway in PAH.

Methods

Health state development

Health state descriptions were drafted based on review of the literature and interviews with three clinical experts. Two clinical experts were pulmonary hypertension clinical nurse specialists who work directly with PAH patients in the UK and Ireland. The additional clinical expert was an internal employee who previously worked as a pediatric cardiologist and now works as a medical affairs specialist at Actelion. The interviews followed semistructured interview guides and focused on patients' experiences with PAH as a disease, as well as with different PAH treatments. All clinical experts then later reviewed and provided comments on the draft health states in order to validate the content. Minor revisions to the health states were made based on these comments. Health state content was also informed and validated based on review of the literature, published clinical guidelines,[10] and treatment instructions for use. Literature searching targeted published research related to symptoms and impacts of PAH,[29–32] and also included research conducted directly with patients and carers.[13,20]

Each of the health states contained an identical description of the disease, symptoms, and impacts of PAH but differed in the description of the treatment mode of administration. Health states were intended to be read and valued by the

general public, and therefore contained language that could be understood by adults without any clinical background. The health states were labeled with arbitrary symbols and did not include a disease label in order to avoid any possible distortion in health state evaluation on account of preconceived conceptions of the disease.[33] In addition to the health states, a support document was developed that included pictures and further descriptions of the treatment modes of administration. This was designed to help participants fully understand what the different treatment devices involve in terms of preparation, drug administration, device cleaning, and patient care. This document was developed primarily using treatment instructions for use and was also reviewed by the clinical experts.

Pilot interviews and final health states

The draft health states and the support document were piloted with 10 members of the UK general public to ensure the content was clear and would be understood during valuation. Participants were asked to complete an in-person time trade-off (TTO) exercise (detailed in the "Health state valuations" section), followed by cognitive interview questions about the TTO exercise and study materials (including each health state). The interviews took place in two waves (n=5 per wave) to allow for the identification and cognitive testing of any revisions to the vignettes and support document indicated from the first wave of interviews. The health states and support document were found to be understood by all of the participants and therefore deemed suitable for use in the valuation exercise, with only minor formatting issues identified by piloting (ie, font size and text alignment) addressed before being finalized.

The final health states are shown in Table 1, and an example is shown in Table 2. The four health states comprised identical descriptions of PAH as a disease, the main symptoms, and impacts, but differed in treatment description (twice daily oral drug, nebulization, continuous subcutaneous infusion, or continuous intravenous infusion with a permanent catheter).

Table 1 Final health states

Mode of administration	Agent
Twice-daily oral drug	• Selexipag (Uptravi®)
Nebulization	• Iloprost (Ventavis®)
Continuous subcutaneous infusion	• Treprostinil (Remodulin®)
Continuous intravenous infusion with a permanent catheter[a]	• Epoprostenol non thermostable (Flolan®) • Epoprostenol thermostable (Veletri®, Flolan pH12®) • Treprostinil (Remodulin®)

Notes: [a]Three different products are available via this mode of administration. There are minor differences between the three formulations. Epoprostenol thermostable was used as the reference case for development of the health state.

Participants

Pilot interviews were conducted with 10 members of the UK general public based in London by two experienced field interviewers. Participants were recruited by a member of the ICON project team using an advertisement posted on community noticeboards and online. Inclusion criteria were aged 18 years and over; currently resident in the UK; able to read and speak English and able to communicate well with study staff; able to understand the valuation exercise as judged by the interviewer; and willing to provide informed consent. Pilot interviews were audio recorded with permission from the participants for reference purposes only. Participants could refuse permission for audio recording without penalty, and could still participate in the interview. Interviews took place in private meeting rooms at times convenient to the participants. All participants provided written informed consent to participate in the interviews.

Final health state valuation was conducted with 150 members of the UK general public based in Bristol, London, Marlow, and Sheffield. Participants were recruited using an advertisement posted on community noticeboards and online by six experienced field interviewers. Inclusion criteria were the same as for the pilot interviews. Interviews took place in private meeting rooms at times convenient to the participants. All participants provided written informed consent to participate in the valuation and interviews were not recorded.

Health state valuation

Following consent, participants completed a sociodemographic questionnaire, used for the purposes of sample description, and the EQ-5D-5L. The EQ-5D-5L instrument is a self-administered generic preference-weighted QoL measure that can be used to determine each individual's current health state utility.[34] The instrument comprises five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each with five levels. A single utility score can be derived from the instrument using a published UK algorithm.[34] The instrument also includes a 100-point visual analog scale (VAS) from 0 (worst health imaginable) to 100 (best health imaginable), which asks participants to rate their own health on the day they participated in the study.

A rating exercise using the health states was then completed to familiarize the participants with the individual descriptions. Participants were presented with one health state at a time in a random order and asked to rate each of the

Table 2 Example health state

Δ	
Disease	• You have a condition which means you have high blood pressure in your lungs. This puts a strain on the right side of your heart as it has to work harder to push blood through the lungs to pick up oxygen.
Main symptoms	• You often feel tired. • You find it difficult to breathe (experience shortness of breath) when you climb stairs and cannot keep up with others when walking on the flat. • You often feel light-headed (dizzy) when you stand up. • You can sometimes experience pain and a feeling of tightness in your chest when undertaking exercise such as walking at the same pace as others on the flat (level ground) or carrying shopping.
Impacts	• You cannot do things in the house that need a lot of physical effort such as vacuuming, carrying shopping, or gardening. • You are able to work, but you cannot do anything at work that involves a lot of physical exertion, such as carrying heavy objects. • You are able to socialize, but you cannot do sports or physical activities that involve a lot of physical exertion. • You are able to travel for work or holidays but this needs to be planned in advance and routes that involve stairs and a lot of walking will be more difficult.
Treatment	• Every 3 months you have a medical assessment involving blood tests. This takes about half a day. • To stabilize your symptoms and to prevent your condition from getting worse, you are treated with medication. • You need to take 2 types of tablets each day. ○ Tablet 1 needs to be taken twice a day. ○ Tablet 2 needs to be taken three times a day. • You also take a medication that is delivered directly into your bloodstream through a narrow, flexible tube called a catheter. This is inserted under local anesthetic into a vein leading to your heart. • The catheter is linked with a thin tube to a plastic container of the drug fixed to a pump, which you need to carry with you at all times. The pump is about the size of a calculator and weighs approximately 400 g (about the weight of a tin of beans). • To have the catheter inserted, and to learn how to prepare the plastic containers and use the pump, you stay in hospital for 7 days. • You should not get the pump wet, so you should protect this with a waterproof covering when showering. You should not go swimming with the pump. • Once you have learnt how to get the medication ready, you can fill seven plastic containers needed for a week on the same day, and store them in the fridge. This takes you about one hour. • You need to change the medication plastic container daily. This takes about 10 minutes. • The catheter site needs to be cleaned carefully at least once a week so that it does not get infected. The cleaning takes about 5–10 minutes.

health state vignettes. This exercise comprised the placing of cards describing each of the health states on an enlarged 100-point VAS, where the anchors of 0 and 100 were worst and best imaginable health, respectively. Two additional health states describing being in full health and being dead were also rated.

A TTO exercise was then conducted to elicit utility values for each health state. The TTO method, in deriving utility values based upon participants' responses to decision scenarios, was specifically developed for use in health care.[35] Health states were presented to the participants in a random order and the values elicited were noted by the interviewer. The TTO exercise used a board with two hypothetical life choices representing number of years in full health and number of years in a health state, up to a total time of 10 years. Respondents were presented with a series of two choices, and asked to choose their preference between living in the health state for 10 years or living in a state of full health. Time in full health was then varied in 6-month increments until the participant was indifferent between the two choices. The utility is calculated by dividing the time in the full health state by the time in the presented health state, so that the formula can be described as: Utility = years in full health/years in health state. For this study, a maximum total life time horizon of 10 years was chosen in line with the UK measurement and valuation of health study[36] and because it is most commonly used in TTO studies in other chronic diseases.[37,38]

The lead-time (LT-TTO) approach was utilized for any health state considered by a participant in the TTO exercise to be worse than dead (ie, where on the initial TTO exercise the participant preferred to be dead than to live for 10 years in a health state). The LT-TTO methodology presented participants with a scenario where they could choose between a life comprising full health for a maximum of 10 years followed by immediate death (where the amount of time spent in full health varies), or a life comprising living in full health for 10 years followed by living in the health state for 10 years, and then immediate death. When a participant became indifferent between the two choices, a utility value for that

health state was calculated as follows: Utility = (years in full health – years of lead-time)/years in health state.[39]

Analysis

Basic descriptive statistics (mean [standard deviation], N [%]) were used to describe the sociodemographic characteristics of the study sample, including their EQ-5D-5L scores, VAS scores and utility values of health states, as well as to compare the study sample values to EQ-5D-5L and UK published norms.[40] Mixed and general linear models were used to compare VAS and utility scores between health states, with post hoc tests (eg, Dunnett's test with the oral health state taken as reference) used to compare VAS ratings and utility scores between health states. Univariable and multivariable mixed effects regression models were used to assess relationships between sociodemographic variables and VAS ratings and utility values, with results presented as unadjusted and adjusted regression coefficients (β) with standard error (SE). Throughout, 95% confidence intervals (CIs) were used to express uncertainty in the data, with statistical significance taken at the 5% level ($p<0.05$).

Ethics approval

This study was approved by Salus IRB on April 27, 2017 (protocol #0179–0042).

Consent for publication

The information presented in this manuscript has been sufficiently anonymized, and so it is not possible to obtain consent for publication from the participants of this study.

Results

Sample description

A total of 150 members of the general public valued the health states (mean age 37.2 years; 62.7% female). The sample characteristics and EQ-5D-5L results of those completing the health state valuation exercises are shown in Table 3.

The study sample was compared with the UK general population.[40–43] There were some differences with the study sample having higher numbers of females (62.7% compared with 50.8%) and a lower median age (33.5 years compared with 40 years). The ethnicity of the sample was more diverse, with 71.3% reporting as White ethnicity compared with 85.9% in the general population. A lower proportion of the participants were employed with a higher proportion being students and single than the general population, which is likely to reflect the younger age of this sample. The mean state of health, as measured by the VAS, was slightly lower in the study sample than UK norms (81.5 vs 82.8).

Table 3 Sociodemographic and EQ-5D-5L results

Demographic	Study sample (n=150)	UK population[a]
Sex (%)		
Male	56 (37.3%)	49.2%
Female	94 (62.7%)	50.8%
Median age (mean, SD), years	33.5 (37.2, 14.3)	40.0
Range, years	18–74	–
Ethnicity (%)[b]		
White	107 (71.3%)	85.9%
Mixed race	11 (7.3%)	2.2%
Asian	14 (9.3%)	7.5%
Black	15 (10.0%)	3.4%
Other/Middle Eastern	2 (1.3%)	0.6%
Prefer not to answer	1 (0.7%)	–
Employment status (%)		
Employed full time	55 (36.7%)	55.2%
Employed part time	32 (21.3%)	19.7%
Student	22 (14.7%)	4.9%
Seeking work	6 (4%)	–
Unemployed	5 (3.3%)	6.3%
Retired	7 (4.7%)	–
Self-employed	16 (10.67%)	13.9%
Stay at home	4 (2.7%)	–
Other	3 (2%)	–
Qualifications (%)		
No qualifications	3 (2.0%)	22.7%
Qualifications (non-university)	63 (42.0%)	50.2%
Qualifications (university)	84 (56.0%)	27.2%
Marital status (%)		
Single	65 (43.3%)	34.6%
Partner/married	76 (50.7%)	46.8%
Divorced/separated/widowed	9 (6.0%)	18.6%
Children, n (%)		
Yes – have children	59 (39.3%)	–
No – do not have children	91 (60.7%)	–
Median number of children as dependents (SD)	1 (0.95)	–
Other dependents, n (%)		
Yes – have other dependents	7 (4.7%)	–
No – do not have other dependents	143 (95.3%)	–
EQ-5D-5L scores[c]		
Dimension scores, n (%) > none		
Mobility	17 (11.3%)	623 (18.4%)
Self-care	6 (4.0%)	144 (4.3%)
Usual activities	23 (15.3%)	551 (16.3%)
Pain/discomfort	45 (30.0%)	1,117 (33.0%)
Anxiety/depression	37 (24.7%)	710 (21.0%)
EQ-5D index score, mean (SE)	0.90 (0.01)	0.86 (<0.01)
EQ VAS score, mean (SE)	81.5 (1.25)	82.8 (0.4)

Notes: [a]Sex and age data from Overview of the United Kingdom (Office for National Statistics 2015).[41] Ethnicity, qualifications, marital status, and religious status data from UK Census data (Office for National Statistics, 2011).[42] Employment data from UK Statistical Bulletin (Office for National Statistics, 2016).[43] [b]One participant was both Black/African/Caribbean/Black British – African and Black/African/Caribbean/Black British – Caribbean. One participant was both White – English and Black/African/Caribbean/Black British – Caribbean (and categorized as being of mixed race). [c]Study sample using the EQ-5D-5L. UK norms using the EQ-5D-3L.[40]

Abbreviations: SD, standard deviation; SE, standard error; VAS, visual analog scale.

Health state valuations

The mean observed TTO and VAS utility scores for the PAH health states are presented in Figures 1 and 2, respectively. The oral treatment administration health state received the highest mean ratings in the VAS exercise (67.2 [19.1]) and the highest mean TTO utility value (0.85 [0.16]). By contrast, intravenous treatment administration received the lowest VAS rating (30.8 [17.0]) and TTO utility value (0.54 [0.32]). The VAS and TTO scores differed statistically significantly between the health states (both $p<0.001$).

The disutility of each health state rating was computed by subtracting the mean rating of the oral treatment administration health state from the mean rating of each of the other health states (Figure 3). The greatest mean disutility value was for the intravenous treatment administration health state at −0.31 (0.29), with the least disutility value for inhaled treatment administration at −0.11 (0.20).

In terms of TTO utility scores, the univariable mixed model analyses showed that there were two sociodemographic factors with significant associations: age group and having child dependents (Table 4). In terms of age group, those in the highest age group (43–74 years) had higher mean scores than those in the youngest age group (18–28 years) (mean=0.11, p=0.04). In terms of child dependents, those with dependents had higher mean scores (mean=0.12, p=0.01). However, after adjusting for the effects of all other factors in multiple variable mixed effects regression models, only the effect of having child dependents remained significant, with these participants giving higher mean scores (mean=0.10, p=0.04). There were no significant associations, in terms of TTO utility scores, for the other sociodemographic factors (sex, ethnicity, employment status, education, marital status). The univariable mixed model analyses also indicated that there was one sociodemographic factor with a significant association with VAS scores: having child dependents. Participants with child dependents had higher mean scores than those without (mean=6.83, p=0.014). There were no significant associations, in terms of VAS scores, for the other sociodemographic factors (sex, age group, ethnicity, employment status, education, marital status, religious status).

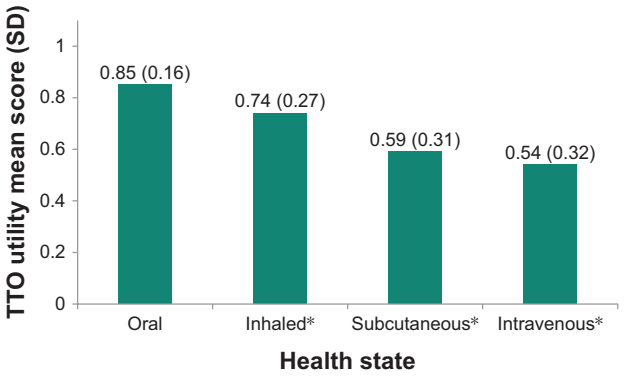

Figure 1 Mean TTO utility scores for each PAH health state.
Notes: *p-value vs oral health state; $p<0.001$; mixed model $F = 92.4$, $p<0.001$.
Abbreviations: PAH, pulmonary arterial hypertension; SD, standard deviation; TTO, time trade-off.

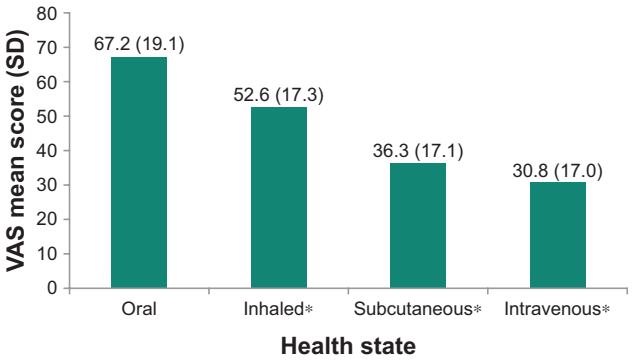

Figure 2 Mean VAS utility scores for each PAH health state.
Notes: *p-value vs oral health state; $p<0.001$; mixed model $F = 326.5$, $p<0.001$.
Abbreviations: PAH, pulmonary arterial hypertension; SD, standard deviation; VAS, visual analog scale.

Discussion

The aim of this study was to elicit robust utility values associated with health states corresponding to different modes of oral and non-oral treatment administration of drugs acting on the prostacyclin pathway in PAH. The results show that the oral treatment administration health state was the most preferred, with intravenous administration being the least preferred. The differences between the utilities indicate

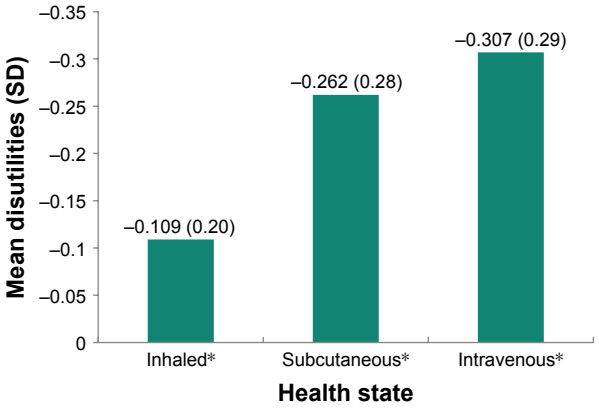

Figure 3 Mean disutilities of TTO utility scores for each non-oral vs oral PAH health state.
Notes: *p-value vs oral health state; $p<0.001$.
Abbreviations: PAH, pulmonary arterial hypertension; SD, standard deviation; TTO, time trade-off.

Table 4 Results from the univariable and multivariable mixed effects regression models of TTO utility scores, with *p*-values significant at $p<0.05$ indicated in bold

TTO scores (N=150)	Univariable β (SE)	*p*-value	Multivariable Adj β (SE)	*p*-value
Sex				
Female vs male	0.065 (0.038)	0.088	0.037 (0.040)	0.360
Age group		0.042		0.290
43–74 vs 18–28 years	0.109 (0.044)	0.015	0.094 (0.055)	0.092
29–42 vs 18–28 years	0.026 (0.044)	0.551	−0.004 (0.053)	0.941
Ethnicity				
White vs non-White	0.024 (0.041)	0.568	−0.004 (0.045)	0.932
Employment status				
Employed vs not	−0.041 (0.040)	0.304	−0.087 (0.045)	0.054
Education		0.169		
No qualifications vs university	0.232 (0.132)	0.082	–	–
School/college vs university	−0.019 (0.037)	0.612	–	–
No/school/college vs university	−0.008 (0.037)	0.838	−0.053 (0.041)	0.205
Marital status		0.141		0.783
Divorced/separated/widowed vs single	0.110 (0.080)	0.169	0.012 (0.090)	0.893
Married/partner vs single	0.066 (0.038)	0.084	0.032 (0.046)	0.493
Religious status		0.603		0.822
Prefer not to answer vs no	−0.064 (0.083)	0.443	−0.051 (0.090)	0.570
Yes vs no	−0.034 (0.045)	0.458	−0.018 (0.049)	0.715
Child dependents				
Yes vs no	0.116 (0.042)	**0.006**	0.103 (0.049)	**0.035**
Other dependents				
Yes vs no	−0.018 (0.088)	0.838	−0.057 (0.092)	0.538

Abbreviations: SE, standard error; TTO, time trade-off.

that oral mode of treatment administration is perceived to be associated with a significantly better state of health than the three other modes of treatment administration. In addition, the values show the order of preference following the oral state to be inhaled, followed by subcutaneous, with intravenous administration being the least preferred.

Evaluation of the relationships between population demographic characteristics and utility scores was completed using mixed model analyses, which showed that participants with children had higher mean utility scores, indicating that having child dependents could influence the amount participants are willing to trade. They also had higher mean VAS scores than those without children. This observation is in line with findings from a study by van Nooten et al, in which respondents with children traded off fewer years than those without when valuing health states of varying severity.[44] In this study, factors associated with TTO responses were explored, with participants with children indicating that when completing the TTO exercise they were thinking about reaching a particular time or life event, typically related to children and grandchildren (such as seeing them grow up, being at their children's wedding, living long enough for children to become independent), whereas those without children gave reasons related to having a family.[44] The findings of the current study suggest that more research should be done to explore the various factors that may influence TTO responses, and in particular whether or not characteristics such as having dependent children need to be taken into account when estimating utilities.

Although there are no studies in the literature that provide utilities and disutilities for treatment modes of administration related to PAH, attempts were made to compare the disutility values derived from this study with the wider literature associated with treatment modes of administration in other diseases. Regarding subcutaneous mode of administration utilities, a study comparing iron chelation therapy (deferasirox) administered via subcutaneous infusion with once-daily oral medication reported a mean disutility value from oral to subcutaneous of −0.23,[45] similar to but slightly less negative than the −0.26 found in this study. This is consistent with the properties of the two treatments, with both causing infusion site pain but with deferasirox being administered 8−12 hours per day, 5−7 days a week,[45] while the subcutaneous treatment for PAH (treprostinil) is administered continuously. Additionally, it was considered that our results could arguably be compared to published utilities for insulin pumps used in the

treatment of diabetes.[46] However, there are two main factors that make this comparison unsuitable. First, the pump for continuous subcutaneous infusion used to treat PAH, unlike in insulin treatment for diabetes, cannot be removed for a period of time.[47] Second, and perhaps more importantly, infusion site pain is more frequent and much more intense than with the continuous infusion of insulin.[48]

Regarding comparison to intravenous infusion in other diseases, a study was identified that provided a disutility for once-daily intravenous infusion of ganciclovir used as therapy for AIDS-related cytomegalovirus retinitis.[49] The study reported a mean disutility value of −0.22, which is different from the −0.31 value elicited in this study. However, it is reasonable to conclude that these disutilities are not directly comparable as receiving an intravenous infusion once daily is not equivalent to continuous intravenous infusion in terms of overall treatment burden. Regarding comparability of intravenous treatments, the most comparable treatment modality to intravenous prostacyclin would be the use of left ventricular assist devices (LVADs) as they require continuous use and intravenous lines, similar to the intravenous treatment for PAH.[50] However, there are no existing utilities in the literature for LVADs.

Regarding published disutility values for inhaled vs oral treatment administration, it is not possible reasonably to compare the inhaled treatment related to PAH to inhaled treatments used to treat other chronic conditions such as asthma or type 2 diabetes. This is because the preparation, inhalation, and cleaning processes for PAH inhaled treatments require substantially more time (approximately 15 minutes every 2–3 hours, 6–9 times per day) and rigor (washing and drying all parts of the nebulizer device at the end of each day, as well as boiling some parts of the device once per week) than other forms of inhaled medicines.[51]

This study elicited utilities using TTO methodology, which is well suited to isolate utilities associated with treatment administration, and has been used in other similar study designs.[45,49,52–55] However, while the study yielded logical results, with differences between the utilities being in the expected direction, there are some limitations with the study methods that should be highlighted and addressed. The robustness of utilities associated with hypothetical health states is limited by the accuracy of the health states, meaning utilities obtained from participants responding to hypothetical health states might be different from those obtained directly from patients. In this study, the general population was used to value the health states in order better to approximate the societal viewpoint as suggested in the guidance from some health technology assessment bodies.[23–25] This methodology could be replicated and used with PAH patients in future research if required. In this study, the health state descriptions of injectable and subcutaneous were developed to represent external pumps that would typically and commonly be used in clinical practice. There are a small number of expert PAH centers that use implantable pumps to administer intravenous treprostinil. These could potentially reduce some of the risks or impacts related with the devices described in this study.[56,57] However, implantable pumps require a general anesthetic to implant and are not suitable for all patients. Therefore, vignettes specifically to describe administration with an implantable pump were not developed for this study.

Another study limitation is related to the study sample. Although efforts were made to balance the sample in terms of demographic factors such as age, sex, and ethnic or racial background, the sample was not intended to be nationally representative. Comparisons between the sample and the UK general population found that the participants of this study were younger on average, had a higher percentage of females, and were more ethnically diverse. Similarly, the requirement of attending an in-person interview could have unwittingly biased the sample towards being healthier than the general population. However, there is no reason to believe that the values elicited in this study would be consistently different from values from a nationally representative sample.

Conclusion

This study provides the first set of utility values for modes of administration of PAH drugs acting on the prostacyclin pathway. The results of this study suggest that there are quantifiable HRQL differences perceived between different modes of administration of these drugs.

Data availability

Only SL, CEK, and HAD had access to patient identifying data. Interview data is identifiable only by an ID number and is stored separately from personally identifiable information (eg, consent documents). No additional unpublished data were collected during the study.

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Author contributions

EWD and AB contributed to study design, data analysis and interpretation, and drafting or revising of the manuscript. SL, CEK, and HAD contributed to study design, data collection, data analysis and interpretation, and drafting or revising of the manuscript. WGS contributed to study design and drafting or revising of the manuscript. All authors approved the final version of the manuscript for publication, and agree to be accountable for all aspects of the work.

Disclosure

HAD, CEK, and SL are employees of ICON plc. AB and EWD are employees of Actelion Pharmaceuticals Ltd. AB owns stock or options. WGS has received honorarium for speaking and consultancy from Actelion Pharmaceuticals, Bayer AG, GlaxoSmithKline, and United Therapeutics. The authors report no other conflicts of interest in this work.

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