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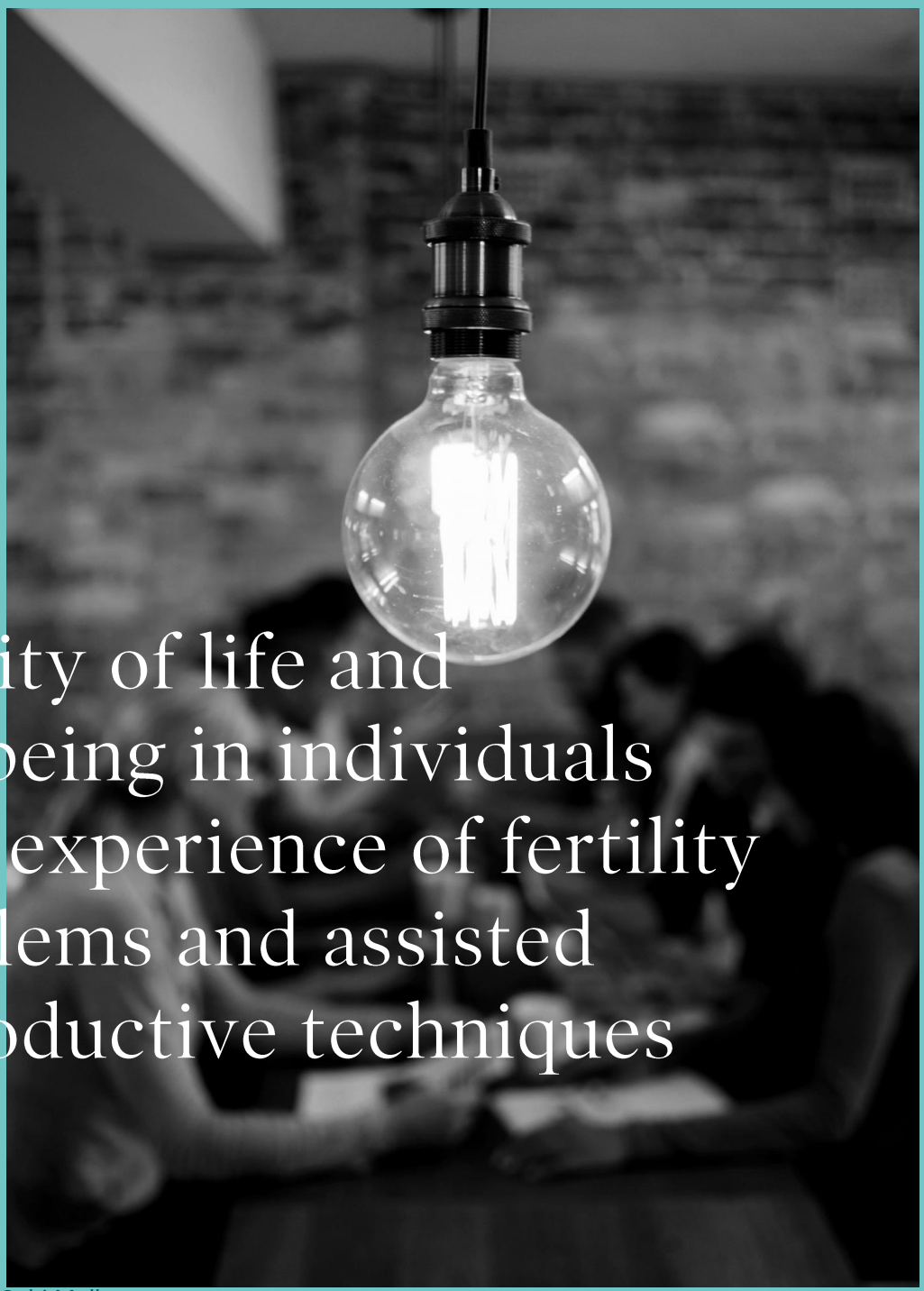

Quality of life and wellbeing in individuals with experience of fertility problems and assisted reproductive techniques

RESEARCH PAPER
JULY 2022

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Steering Group

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Jane Blower, Jacky Boivin, John E Brazier, Gwenda Burns, Aina Canyelles Vingut, Sofia Gameiro, Hareth Al-Janabi, Marie Markert, David Parkin, Jose Luis Pinto-Prades, Christina Tranda

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Executive summary

Introduction: Appropriately assessing the costs and consequences of providing treatment for infertility is becoming ever more important. Nearly all European countries are experiencing long-term downward trends in population fertility, and it is expected that the number of people seeking treatment for infertility will increase in the coming years. Fertility treatments, collectively termed Assisted Reproductive Techniques (ART), are now widely available for routine clinical use. However, there is a lack of cost-effectiveness evidence for fertility treatments. This, in part, reflects challenges associated with estimating the health-related quality of life (HRQoL) impacts of infertility and subfertility.

Aims: The primary aim of this study was to estimate HRQoL for three groups of individuals with infertility or subfertility who: a) did not have access to ART treatment (or had suboptimal access) and did not have a successful pregnancy; b) had access to at least three cycles of ART but did not have a successful pregnancy; and c) had access to at least three cycles of ART and had a successful pregnancy. We also recruited a control group consisting of individuals who did not experience fertility problems and had a baby as a reference point to test the face validity of our utility estimates. A second objective was to compare the sensitivity of several patient-reported outcome measures for assessing HRQoL in the context of assessing ART. We identified EQ-5D-5L and EuroQol Health and Wellbeing instrument (EQ-HWB) as the most appropriate instruments in this context. We also want to determine whether the EQ-5D-5L is sensitive to differences in infertility HRQoL by using a validated disease-specific instrument (FertiQoL) and comparing the EQ-5D-5L performance to that of the FertiQoL. Our study seeks to inform future HTA bodies on assessing the effectiveness of ARTs.

Methods: Individuals from the UK were invited to complete an online survey. Participants were recruited by a survey firm and categorised into our groups of interest using screening questions. All participants completed the EQ-5D-5L instrument as well as the recently developed generic EQ-HWB. Except for those in the control group, all individuals also completed the condition-specific FertiQoL instrument. Utilities were estimated for the EQ-5D-5L only, as a value set for the EQ-HWB is still in development. A summary score for EQ-HWB and the FertiQoL Core score was also examined. Comparisons of mean values in each group were made, controlling for age, sex, and a number of additional socioeconomic factors. Comparisons were also made of mean scores based on different times since respondents' most recent pregnancy attempt. Results were contrasted with the evidence identified from the psychology literature on infertility.

Results: Overall, the mean scores suggest that those with fertility problems with a successful ART treatment have worse HRQoL (EQ-5D values) than those who did not use ARTs. This difference holds in all the time segments. Those with a successful ART treatment (at least one child) also report worse HRQoL than those with children who did not have fertility problems. In the long run, assessments provide more similar scores for the three groups. A similar pattern was observed for EQ-HWB scores and FertiQoL Core scores among those who had their last pregnancy attempt up to five years ago. The relation is partially reversed six years after the treatment, where those who had a successful ART treatment can show slightly better outcomes than those with fertility problems who did not use ARTs for most of the time segments. This result is more consistent with the previous literature on QoL, suggesting that EQ-HWB and FertiQoL scores seem to reflect better QoL in the long run.

Conclusion: HRQoL measures provide a counter-intuitive result, implying the "irrationality" of ART. Broader generic or condition-specific measures of HRQoL (such as EQ-HWB and FertiQoL, respectively), which add wellbeing dimensions to the outcome description, show a better correspondence with evidence from the psychology literature. However, results are still not fully reversing the ordering of the groups in our study. Future research should elucidate whether a "health-related" measure of QoL could sufficiently capture the effects of infertility, or otherwise relevant dimensions of the impact of infertility on the individual have to be compromised. Further comparisons would be beneficial when a value set for EQ-HWB becomes available to test the robustness of this conclusion.

1. Introduction

The population of the United Kingdom (UK) and most developed countries is ageing, meaning that the population aged 65 years and over is growing faster than other age groups. This fact is having significant socioeconomic impacts, such as adding pressure to increase health and social care expenditures and jeopardising pension systems' sustainability. The reasons behind the ageing population are varied. However, a principal contributor to the ageing in these countries is the long-term downward trends in fertility, partly because the age at which a woman has her first child has been rising, and so has her partner's age.[1] At an older age, infertility problems become more frequent. Thus, the number of couples experiencing infertility is expected to increase in the coming years, e.g., due to lifestyle changes.[2]

Several fertility treatments, including Assisted Reproductive Techniques (ART), are now widely available for routine clinical use. Treatment possibilities cover a range of interventions (e.g., In Vitro Fertilisation [IVF], Gamete intra-Fallopian Transfer, and Intracytoplasmic Sperm Injection), all of which have the goal of assisting patients to become pregnant and deliver a live infant.[3] There is currently a strong growth in the IVF market, driven by the increasing incidence of infertility – in the UK alone, home to around 80 IVF clinics, the number of cycles performed rose from 18,000 in 1992 to 63,573 in 2014[4].

Infertility is considered a disease.[5] Despite this, policymakers have tended to view fertility treatment as discretionary and expensive, and there is an ongoing debate regarding the allocation of finite resources in this area and the appropriate balance of costs borne by individual patients and society.[6] At present, different countries pursue different policies regarding which treatments, if any, are publicly funded. In many cases, technology adoption decisions have been made in the absence of robust cost-effectiveness analysis. Therefore, appropriately assessing the costs and consequences of providing infertility treatment is becoming ever more critical.

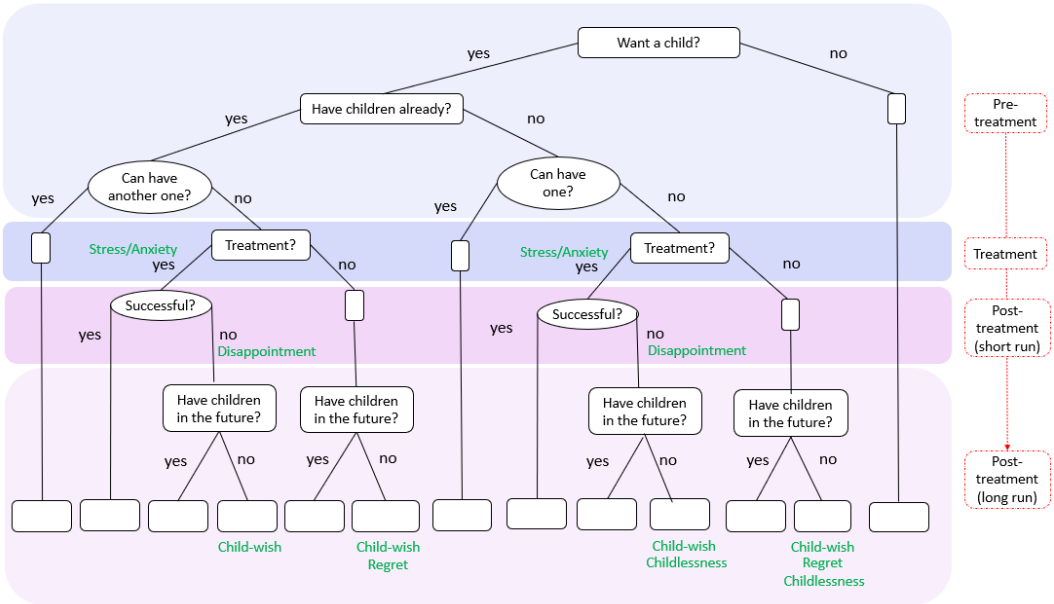
Health Technology Assessment (HTA) bodies in charge of approving and/or funding fertility treatments (e.g., the National Institute for Health and Care Excellence (NICE) in England and Haute Autorité de Santé (HAS) in France) request utility data, preferably captured using health-related quality of life (HRQoL) generic instruments such as the EQ-5D, SF-6D, or HUI-II. HRQoL measures combined with estimations of the quantity of life (number of years) generate Quality-Adjusted Life Year (QALY). HTA bodies such as NICE or HAS assess the cost-effectiveness of new technologies in cost-per-QALY. Notwithstanding, evidence on the effectiveness and cost-effectiveness of ARTs is very limited. We have only identified two primary references assessing the utility gains of fertility treatments. Both of these estimates represent utility at a single point in time, with no consideration of the duration of impact, and they do not address the impact of successful or unsuccessful fertility treatment on utility.

The first reference is a United States (US) report on Vaccines, where 'Infertility' was considered a potential morbidity scenario (with an average duration of 22 years) in women for infections such as chlamydia. In the reported study, a committee was asked to assign a health state level for each of the seven attributes of the HUI-II instrument. The utility weight of the agreed HUI-II health profile (0.82) was obtained from a Canadian value set.[7] With the use of population norms as a reference, the utility value 0.82 in the US is reinterpreted as a utility decrement of 0.07 for being 'infertile with the desire for a child' in the UK by Scotland et al.[8] The same value, 0.07, is also adopted by NICE to assess the cost-effectiveness of fertility treatments in the Clinical guideline CG156,[9] recognising that the estimate may not be robust.

The second reference we identified identifies utilities for infertility in the range of 0.792 to 0.868.[10] The utility values were elicited from the Dutch population through a Time-Trade Off task in which the health state 'Infertile' was described as being in full health (no problems in any of the dimensions of EQ-5D) plus being infertile with the desire of one or more children. Note that the paper framework assumes that infertility impacts the quality of life (QoL) through mechanisms beyond mobility, self-care, usual activities, pain, discomfort, anxiety or depression- which implies that HTA bodies such as NICE could consider being infertile as equivalent to being in full health

The use of the QALY is desirable because it provides a 'common currency' that can be used to compare different disease areas. However, it is challenging in this context because the value associated with infertility care cannot easily be captured using the underlying quality-of-life–length-of-life framework. While the EQ-5D may be appropriate for estimating the short-term physical and emotional HRQoL impacts of infertility treatment, which tend to cause physical and emotional discomfort, it is less likely to be sensitive to the long-term effects of infertility and childlessness. Literature in psychology has demonstrated that going through a fertility treatment involves a complex array of challenges that are triggered at different stages of the process: challenges to getting and accepting diagnosis; deciding to go through fertility treatment; stressful and burdensome procedure; if successful, experiencing a pregnancy (associated with lower HRQoL measures)[11], giving birth and having toddlers at home; if unsuccessful, disappointment, child-wish, childlessness and adjustment; if no treatment was sought, regret.[12] Consequently, the psychology literature assesses the impact of achieving parenting goals' versus not at different time points in the lifepath of those with infertility problems using a wide variety of patient-reported outcome measures (PROMs), such as SF-36[13–16] GHQ-12 and GHQ-28,[17,18] Hopkins Symptom Checklist,[19] Life Satisfaction,[17,20,21] State and Trait Anxiety Inventory and Beck Depression Index,[22,23] Wellbeing,[24,25] and FertiQoL.[18] (See Figure 1 for a scheme of the scenario complexity). Note that while some of these measures are attached to value sets that could be applied in cost-utility studies, however, none of these studies reported outcomes in terms of utilities.[26]

FIGURE 1: STAGES AND PSYCHOLOGICAL FACTORS RELATED TO ASSISTED REPRODUCTIVE TECHNIQUES (ART).



In this paper, we aim to compare the sensitivity of several PROMs for assessing HRQoL in individuals from the UK who have experienced fertility problems and childlessness and estimate health state utilities. We have identified EQ-5D-5L and EuroQol Health and Wellbeing instrument (EQ-HWB) as the most appropriate patient-reported outcome (PRO) instruments in this context. We also want to determine whether NICE's recommended PRO instrument (the EQ-5D) is sensitive to differences in infertility HRQoL when assessing is using a validated disease-specific instrument (FertiQoL) and comparing the EQ-5D-5L performance to that of the EQ-HWB. Our study seeks to inform future health technology evaluations on the effectiveness of ARTs.

Section 2 sets out the methods used in detail. Section 3 reports the results. Section 4 provides a discussion of the results, and Section 5 concludes.

2. Methods

2.1. Instrument selection

There are a number of generic HRQoL preference-based PROs that could be used to generate health state utilities for use in economic evaluations.

NICE's methodological guidance strongly recommends describing health states using the **EQ-5D** unless there is a compelling reason to believe that it will be inappropriate for a particular condition, where 'inappropriate' is typically interpreted as insensitive to clinically meaningful changes in health for individuals suffering that condition. As such, the EQ-5D was included in the study to provide a baseline against which to compare the other instruments. Specifically, we used the 5L version of the EQ-5D (EQ-5D-5L), as this instrument is more sensitive than the 3L[27]. The recent NICE position statement highlights that either instrument can be used for data collection but that the English 5L value set cannot be used to obtain utilities.

EQ-5D-5L may be appropriate for estimating the short-term physical and emotional HRQoL impacts of infertility treatment, which tend to cause physical and emotional discomfort; however, it is less likely to be sensitive to the long-term effects of infertility and childlessness or 'parenting goals', which are addressed in the psychology literature by means of life satisfaction and wellbeing. Therefore, a plausible *a priori* expectation is that the EQ-5D-5L might be insensitive to changes in the overall QoL of people with fertility problems in the long term. Because of that, the study used an additional generic instrument that combines the two wellbeing elements: the EuroQol Health and Wellbeing Questionnaire (EQ-HWB).

EQ-HWB is arguably the most promising alternative to the EQ-5D for describing the impacts of infertility and childlessness through a generic, preference-based HRQoL measure. The *Extending the QALY* project, supported by NICE and the EuroQol Group, aims to develop a broad measure of HRQoL for use in economic evaluations across health and social care. The crucial advantage of the EQ-HWB for this project is that having been designed to bridge the gap between health and social care, it includes items related to wellbeing not directly related to health (e.g., item 19 'Felt Accepted'). Therefore, it may be more sensitive to the overall impact of infertility than the EQ-5D-5L.

Several other generic, preference-based HRQoL PROs could have been selected for inclusion in the study, including the ICEpop CAPability measure for Adults (ICECAP-A), the Health Utilities Index Mark

2 (HUI-II), and the Short Form 6-dimension (SF-6D). However, none are currently endorsed explicitly by NICE, and all have various limitations of their own:

- The ICECAP-A is a measure of capability (rather than HRQoL), and its value set is not anchored on the full-health-to-dead scale.
- The questions in the HUI-II were not designed for an adult population, although it was used in past NICE infertility guidance[9].
- The 'social functioning' dimension of the SF-6D was considered to be no more sensitive than the EQ-5D-5L at capturing the impacts of infertility and childlessness.

We administered the Fertility quality-of-life (**FertiQoL**) instrument alongside the generic instruments. Whilst there is no clear consensus in the literature regarding the most appropriate condition-specific PRO instrument for capturing the impact of infertility and ART pathways on QoL and wellbeing, a recent review identified the FertiQoL as the most commonly used.[28] FertiQoL was also shown to have adequate face and content validity, acceptable internal consistency reliability, and good construct and known-groups validity.[28] FertiQoL also has the advantage of being mainly an HRQoL measure (although, in terms of convergent validity, FertiQoL has shown higher correlation with mental health measures). However, it also includes items related to QoL that go beyond health and may capture wellbeing traits (e.g., item 14 'Family understanding'). As such, FertiQoL is closer to EQ-HWB than alternative condition-specific HRQoL instruments.

The rationale for including the FertiQoL instrument is to provide data for assessing the sensitivity of the EQ-5D-5L and EQ-HWB instruments. We did not include the optional treatment module. Whilst, *a priori*, FertiQoL might be the most sensitive instrument in capturing fertility-related HRQoL, it is not expected that this will provide a convincing rationale for its use in economic evaluations, not least because it does not have an accompanying value set.

PRO instruments provide rich data, which can be analysed in many ways. However, when contrasting results across groups, as in this study, it is helpful to have some form of summary score or utility.

For **EQ-5D-5L**, it is possible to generate a value for any given response to the five items. These values are regarded as 'utilities' when used in economic evaluation.[29] The recent NICE methods consultation suggests that the new methods guide (currently expected in March 2022) will state that the Decision Support Unit (DSU) algorithm will be the preferred way to obtain utilities for the EQ-5D-5L until a new UK value set becomes available.[30] Therefore, this approach is taken in this study. EQ-5D values are anchored such that 1 is equivalent to full health and 0 is equivalent to being dead, with negative values (indicating a state worse than dead) also possible.

For **EQ-HWB**, a value set for the UK is currently under development, having been delayed by the COVID-19 pandemic. Furthermore, as this instrument is so new, there is little guidance around how to analyse the data to generate a summary score. The approach taken in this study was to sum the individual scores on each item. The best option was given a value of 4, the second-best option a value of 3, and so on until the worst option was given a value of 0. As there are 25 items in the EQ-HWB, this results in a summary score where 0 is the worst and 100 is the best possible. All other possible scores fall somewhere between these two limits.

Finally, for the FertiQoL, each item has a score ranging from 0 to 4. To generate a summary score (the **FertiQoL Core** score), the scores on each item are reversed where necessary, summed, and scaled such that 0 is the worst possible score and 100 is the best possible score. It is worth noting that the FertiQoL is made up of four subscales (emotional, mind/body, relational, social), which can also be examined separately. However, respondents that are not in a relationship do not answer the

questions in the relational subscale. The scaling to generate the FertiQoL Core score omits this section for individuals not in a relationship to ensure that FertiQoL results are comparable regardless of relationship status.

Table 1 provides a summary of the instruments included in the study. EQ-HWB and FertiQoL are typically used as HRQoL instruments. Nevertheless, their most relevant distinction with respect to other instruments is that they define health profiles that include items more typically related to subjective wellbeing (SWB) than to HRQoL. Besides that, the health economics literature generally contemplates 'mental health' as an element of HRQoL; and HRQoL itself as an element of subjective wellbeing. For this reason, we will henceforth use the label 'SWB instrument' to refer to HRQoL instruments that include non-health-related SWB dimensions. Note that any instrument defined to capture SWB will also be labelled as such.

TABLE 1. INSTRUMENTS INCLUDED IN THE STUDY

INSTRUMENT	TYPE	ITEMS	VALUE SET?	RATIONALE FOR INCLUSION
EQ-5D	Generic HRQoL	5	Yes[1]	NICE's recommended measure, according to the current guidance.
EQ-HWB	Generic SWB	25	No[2]	Broader than the EQ-5D - includes wellbeing dimensions
FertiQoL	Condition-specific SWB	26[3]	No	For use as a comparator to test the sensitivity of the other instruments

[1]NICE currently recommends the use of the 3L' crosswalk' algorithm for the EQ-5D-5L[31,32] The recent NICE methods review consultation suggests that the Decision Support Unit (DSU) algorithm will be recommended in the next methods guide until a new 5L value set for the UK is available.[30]
[2]An initial value set is under development and is expected in mid-2022.
[3]Respondents who are not in a relationship must complete six fewer items than those in relationships.

2.2. Survey and data collection

A convenience sample of the general UK population was obtained. The sample was representative of the UK population (>18 years) in terms of age and sex. Respondents were excluded from further analysis if they indicated they never tried to have a baby. Ethical approval was obtained from an independent expert in research ethics, acting under the Association of Research Managers and Administrators (ARMA).

We aim to include individuals who have gone through treatment at different points in the past in order to be able to analyse the correlation between time since treatment and utility decrement.

The online survey comprised several sections:

1. A series of scoping questions (7) were provided to respondents. These questions were used to determine initial eligibility.

2. A participant information sheet (PIS) followed, which provided a plain English summary about the study to support potential participants in their decision to participate in the study or decline participation.

3. An electronic informed consent form (eICF) followed the PIS and was used to record the consent process and participants' agreement to take part in the study.

4. Those who agreed to participate then answered a few screening questions (5) to determine their group.

5. The previously described HRQoL instruments followed. The order of presentation was randomised. The first instrument was either the EQ-5D-5L or EQ-HWB; in all cases, the FertiQoL was presented last to avoid focusing biases that may influence respondents' perception of their health state.

Finally, a series of demographic questions (7) were provided to respondents.

All participants were invited by email and were told they could use a smartphone or laptop to complete the survey. Prior to distribution, the survey instrument was internally pilot tested. The final survey consisted of a total of 75 items. The electronic design of the survey enabled tailoring based on the participant's responses, directing them towards the applicable items. Respondents who answered 'no' when asked if they had experienced fertility problems were included in a baseline reference group that was used to assess the face validity of the results relative to general population estimates of utility. To exclude 'inattentive responders', two minimum completion times were set: two minutes for the control group, who were not required to complete some sections of the questionnaire, and five minutes for the other groups.

2.3. Scenarios

We examine the utility/disutility associated with various scenarios related to infertility, including infertility with no access to treatment (group A); infertility with access to treatment but no successful pregnancy (group B); and infertility with access to treatment and successful pregnancy (group C). As elsewhere in the infertility literature,[28] we distinguished between individuals who had an unsuccessful treatment but had children from those who did not have any children (B+ and B-, resp.). Also, we had two potential control groups: ad-hoc for the study (control) and the general population norms (population). See Table 2 for more detail.

TABLE 2: SCENARIOS RELATED TO INFERTILITY

GROUP	DEFINITION
A	Individuals that have experienced fertility problems but had no/suboptimal access to fertility treatment and who did not have a successful pregnancy
B-	Individuals that have experienced fertility problems and had access to treatment but did not have a successful pregnancy as a result of treatment At the time of the research study, the individuals do not have children
B+	Individuals that have experienced fertility problems and had access to treatment but did not have a successful pregnancy as a result of treatment At the time of the research study, the individuals have at least one child
C	Individuals that have experienced fertility problems and had access to treatment, and did have a successful pregnancy as a result of treatment
Control	Additional individuals who did not have fertility problems will complete HRQoL for comparison purposes only
Population	The general population (with and without fertility problems)

2.4. Analysis

We compare differences in the QoL measures by time since the respondent's most recent pregnancy attempt. The estimates are obtained from Ordinary Least Squares (OLS) regressions. Characteristics that were expected to impact HRQoL were included in the models as either continuous or dummy/indicator variables. A single final specification for each instrument was used to enable easier comparisons between models: controlling for sex, if partner, if dependent children at the time of the last pregnancy attempt, income, education, ethnic group, and if LGBT+.

The psychology literature is used as a reference to formulate our hypothesis on changes in utility along different stages of the fertility treatment experience. Following Kitchen et al.,[28] we explore the assessment of HRQoL/SWB associated with pre-treatment (awareness of being sub-fertile or infertile), treatment, post-treatment short-run (either conception, pregnancy, and neo- and post-natal experience, or disappointment), and in the long run (adjustment vs child-wish, childlessness or regret) (See Figure 1 for an illustration of the selected stages).

A 'snowballing' or 'citation pearl growing'[33] review identified the most relevant papers assessing changes in the health and quality of life (health- and non-health- related) associated with various scenarios related to infertility and ARTs. The information extracted from the literature is summarised in Table 3.

From this exercise, we expected to obtain a priory that:

1. group B would have post-treatment short-run lower utilities than group C;

2. post-treatment long-run utilities of group B+ (unsuccessful treatment with other children) would converge to those of group C; and, finally,

3. post-treatment long-run utilities of group B- (unsuccessful treatment but no other children) would end up being lower than C.

Finally, though we could not obtain evidence for this, we should expect that those infertile individuals that did not have access to treatment (group A) would have lower utilities than the group B- because of the effect of 'regret' (of not having had access to treatment).

TABLE 3: SUMMARY OF RESULTS FROM THE PSYCHOLOGY LITERATURE

			Psychology literature review			
	Time label	Time description	Ref.	Who	What is measured (measure)	Results (group comparison)
Pre-treatment	0	Before infertility diagnosis				
	1	Early stages of infertility management	14	W	Mental health (**MHI-5**)	(A, B-, B+, C) < population
	2	Immediately before treatment	19	W	Health (**SIP**), Anxiety/Depression (**HSCL**)	(B-, B+, C) <= population
			13	All	HRQoL (**SF-36**)	(B-, B+, C) = population
			22	All	Anxiety (**STAI**), Depression (**BDI-PC**)	B- = B+
Treatment	3	During ART	15	All	HRQoL (**SF-36**)	(B-, B+, C) < (A, population)
Post-treatment short run	4	Immediately after treatment-up to 1 year	22	W	Anxiety (**STAI**), Depression (**BDI-PC**)	(B-, B+) < C
			22	M	Anxiety (**STAI**), Depression (**BDI-PC**)	(B-, B+) = C
			23	W	Anxiety (**STAI**), Depression (**BDI**)	C = control
	5	1-2 years after ART	20	W	Life satisfaction	B- = B+ < C
	6	3-5 years after ART	20	W	Life satisfaction	B- < B+ = C
			17	W	Mental health (**GHQ-12**)	(B- , B+) = C
			17	W	Life satisfaction (**SWLS**)	(B- , B+) < C
			25	All	Anxiety (**PGWB**)	B- < control < C
			25	All	Depression (**PGWB**)	B- < control = C
			25	All	General Wellbeing (**PGWB**)	B- < control = C
Post-treatment long-run	7	6-10 years after ART	20	W	Life satisfaction	B- = B+ = C
			24	All	General Wellbeing (**PGWB**)	B- < B+ = C = control
	8	11-20 years after ART	16	W	Mental health (**MHI-5**)	B- < (B+, C)
			21	All	Self-esteem	B- < C
			21	All	Occupational satisfaction	C < B-
			21	All	Life satisfaction	B- = C
	9	More than 20 years after ART				

M: Men; W: women; All: couples
<: worse than; >: better than; =: similar to; ART: Artificial reproduction techniques; HRQoL: Health-related quality of life; SF-36: 36-item Short-Form Health Survey Questionnaire; MHI-5: five-item Mental Health Inventory (part of the SF-36); SIP: Sickness Impact Profile; HSCL: Hopkins Symptom Checklist; STAI: State and Trait Anxiety Inventory; BDI-PC: Beck Depression Inventory for Primary Care; SWLS: Satisfaction With Life Scale; GHQ-12: General health Questionnaire; PGWB: Psychological general wellbeing.
A: infertile/subfertile, no access to treatment, no children; B-: infertile/subfertile, unsuccessful treatment, no children; ; B+: infertile/subfertile, unsuccessful treatment, children; C: infertile/subfertile, successful treatment. Control: fertile.

3. Results

3.1 Respondent characteristics

Table 4 summarises the characteristics of the respondents. After removing participants with negative EQ-5D values,[1] there were a total of 1,575 respondents. There were statistically significant differences between the four groups for all characteristics except for sexual orientation (96-97% heterosexual in all groups). Respondents in group A and the control group were older on average than groups B and C (48-49 vs 40-43), and a higher proportion were male (49-52% vs 20-34%). The date of the most recent pregnancy attempt varied substantially between groups. Most notably, this was within the past 24 months for just under half of respondents in group C, whereas the percentage was around 24% in the control group. In contrast, the date of the most recent pregnancy attempt was over 20 years ago for 42% of the control group, compared with 27% of group A, 13% of group B, and 9% of group C. Whilst there were differences between groups in some characteristics, overall, the majority of respondents were currently in a relationship, had a household income of under £60,000, had some higher education, and were white.

TABLE 4. RESPONDENT CHARACTERISTICS

	Total	A. No/ suboptimal treatment, did not have baby	B. Had treatment, did not have baby	C. Had treatment, had a baby	Control. No fertility problems	p-value
	N=1,575	N=497	N=200	N=378	N=500	
Mean Age (SD)	46 (14)	48 (14)	43 (10)	40 (10)	49 (16)	<0.001
Gender						<0.001
Female	928 (59%)	240 (48%)	133 (67%)	301 (80%)	254 (51%)	
Male	646 (41%)	257 (52%)	67 (34%)	76 (20%)	246 (49%)	
Other	1 (0%)	0 (0%)	0 (0%)	1 (0%)	0 (0%)	
Date of Most Recent Pregnancy Attempt						<0.001
In the past 12 months	336 (21%)	147 (30%)	38 (19%)	78 (21%)	73 (15%)	
In the past 13-24 months	226 (14%)	38 (8%)	44 (22%)	99 (26%)	45 (9%)	
In the past 2 to 5 years	262 (17%)	58 (12%)	52 (26%)	104 (28%)	48 (10%)	
In the past 6 to 10 years	155 (10%)	60 (12%)	16 (8%)	31 (8%)	48 (10%)	
In the past 11 to 20 years	195 (12%)	60 (12%)	25 (13%)	33 (9%)	77 (15%)	
More than 20 years ago	401 (25%)	134 (27%)	25 (13%)	33 (9%)	209 (42%)	
Currently in Relationship						<0.001
Yes	1,393 (88%)	417 (84%)	182 (91%)	362 (96%)	432 (86%)	
No	182 (12%)	80 (16%)	18 (9%)	16 (4%)	68 (14%)	
Sexual Orientation						0.300
Heterosexual or straight	1,521 (97%)	477 (96%)	193 (97%)	367 (97%)	484 (97%)	
Lesbian, gay, bisexual, or transgender (LGBT)	34 (2%)	11 (2%)	4 (2%)	7 (2%)	12 (2%)	
Not listed	7 (0%)	3 (1%)	3 (2%)	1 (0%)	0 (0%)	
Do not know or prefer not to say	13 (1%)	6 (1%)	0 (0%)	3 (1%)	4 (1%)	

[1] Negative values were considered to be mostly likely the result of a condition other than infertility and including them may have biased our results. We decided to drop values classified as 'worse than dead' (n=31; 1.9% of the total sample). As this cut-off point was somewhat arbitrary, we replicated the analysis excluding those individuals with EQ-5D value below -0.1 (n=26; 1.6%), and those below 0.1 (n=49; 3%). No significant change was observed.

	Total	A. No/ suboptimal treatment, did not have baby	B. Had treatment, did not have baby	C. Had treatment, had a baby	Control. No fertility problems	p-value
	N=1,575	N=497	N=200	N=378	N=500	
Household Income						<0.001
Less than £20,000	193 (12%)	83 (17%)	8 (4%)	18 (5%)	84 (17%)	
Between £20,000 and £39,999	437 (28%)	165 (33%)	29 (14%)	62 (16%)	181 (36%)	
Between £40,000 and £59,999	314 (20%)	116 (23%)	23 (12%)	66 (17%)	109 (22%)	
Between £60,000 and £79,999	290 (18%)	63 (13%)	48 (24%)	119 (31%)	60 (12%)	
Between £80,000 and £99,999	180 (11%)	23 (5%)	66 (33%)	68 (18%)	23 (5%)	
More than £100,000	105 (7%)	24 (5%)	23 (12%)	37 (10%)	21 (4%)	
Prefer not to say	56 (4%)	23 (5%)	3 (2%)	8 (2%)	22 (4%)	
Highest Educational Qualification						<0.001
Doctorate	48 (3%)	16 (3%)	1 (1%)	20 (5%)	11 (2%)	
Postgraduate degree	286 (18%)	74 (15%)	19 (10%)	120 (32%)	73 (15%)	
Undergraduate degree	460 (29%)	142 (29%)	81 (41%)	109 (29%)	128 (26%)	
Higher education below a degree	170 (11%)	56 (11%)	23 (12%)	32 (8%)	59 (12%)	
GCE A-Level / AS-Level or equivalent	243 (15%)	83 (17%)	33 (17%)	34 (9%)	93 (19%)	
GCSE grade A*-C / GCE O-Level or equivalent	252 (16%)	81 (16%)	34 (17%)	41 (11%)	96 (19%)	
GCSE grade D-G / CSE or equivalent	73 (5%)	24 (5%)	7 (4%)	17 (4%)	25 (5%)	
Other	11 (1%)	6 (1%)	1 (1%)	3 (1%)	1 (0%)	
No formal qualifications	27 (2%)	13 (3%)	0 (0%)	2 (1%)	12 (2%)	
Prefer not to say	5 (0%)	2 (0%)	1 (1%)	0 (0%)	2 (0%)	
Ethnicity						0.012
White	1,409 (89%)	436 (88%)	185 (93%)	349 (92%)	439 (88%)	
Mixed Race	28 (2%)	7 (1%)	8 (4%)	4 (1%)	9 (2%)	
Asian	88 (6%)	39 (8%)	4 (2%)	12 (3%)	33 (7%)	
Black/African/Caribbean	32 (2%)	8 (2%)	1 (1%)	11 (3%)	12 (2%)	
Arab	5 (0%)	1 (0%)	1 (1%)	0 (0%)	3 (1%)	
Other	2 (0%)	2 (0%)	0 (0%)	0 (0%)	0 (0%)	
Prefer not to answer	11 (1%)	4 (1%)	1 (1%)	2 (1%)	4 (1%)	

Table 5 summarises the fertility treatment experience for respondents from groups A-C, which largely reflects the group definitions (see Table 2). The results show that 84% of group A had no treatment, with the remainder having suboptimal treatment (either diagnostic/early phase treatment only, or <3 cycles of ART treatment). In contrast, and by definition, all respondents in groups B and C had ART treatment, and all respondents in group C had a successful live birth following treatment, whereas those in group B did not.

Table 6 provides the reasons given by individuals in group A regarding why they did not have fertility treatment. Those with (suboptimal) fertility treatment did not answer this question (response 'N/A'). A wide range of reasons were selected, with the most common being that it was unavailable on the NHS and unable to pay for private treatment (n=109; 22%).

TABLE 5. FERTILITY TREATMENT EXPERIENCE

	A. No/ suboptimal treatment, did not have baby	B. Had treatment, did not have baby	C. Had treatment, had a baby
	N=497	N=200	N=378
Fertility Treatment Type(s)[1]			
No treatment	415 (84%)	0 (0%)	0 (0%)
Diagnostic/early phase treatment	51 (10%)	149 (75%)	177 (47%)
Assistive reproductive technologies (ART)	40 (8%)	200 (100%)	378 (100%)
Number of Embryo Transfers/Cycles[2]			
1	14 (3%)	0 (0%)	127 (34%)
2	26 (5%)	0 (0%)	140 (37%)
3	0 (0%)	108 (54%)	79 (21%)
More than 3	0 (0%)	92 (46%)	32 (8%)
Egg/Sperm Donor Used[2]			
Yes	10 (2%)	81 (41%)	232 (61%)
No	26 (5%)	118 (59%)	142 (38%)
Prefer not to answer	4 (1%)	1 (1%)	4 (1%)
Live Birth Following Treatment[3]			
Yes	0 (0%)	0 (0%)	378 (100%)
No	82 (16%)	200 (100%)	0 (0%)

[1]*It was possible to select both diagnostic/early phase treatment and ART.*
[2]*Question only asked to those that had ART treatment.*
[3]*Question only asked to those that had fertility treatment.*

TABLE 6. REASONS FOR NOT HAVING ART TREATMENT

	A. No/suboptimal treatment, did not have baby
	N=497
N/A	40 (8%)
It could be provided by NHS, but not possible due to medical reasons	44 (9%)
It could be provided by NHS, but not possible due to eligibility/NHS requirements	63 (13%)
Not available on NHS, and did not want to pay for a private clinic	109 (22%)
Not available on NHS, and not aware of treatment options at private clinics	70 (14%)
I did not want it due to possible side effects	96 (19%)
I did not have it because job situation did not allow it (economic stress)	41 (8%)
It did not want it due to being afraid that others could tell that they were on fertility treatment (social stress)	34 (7%)

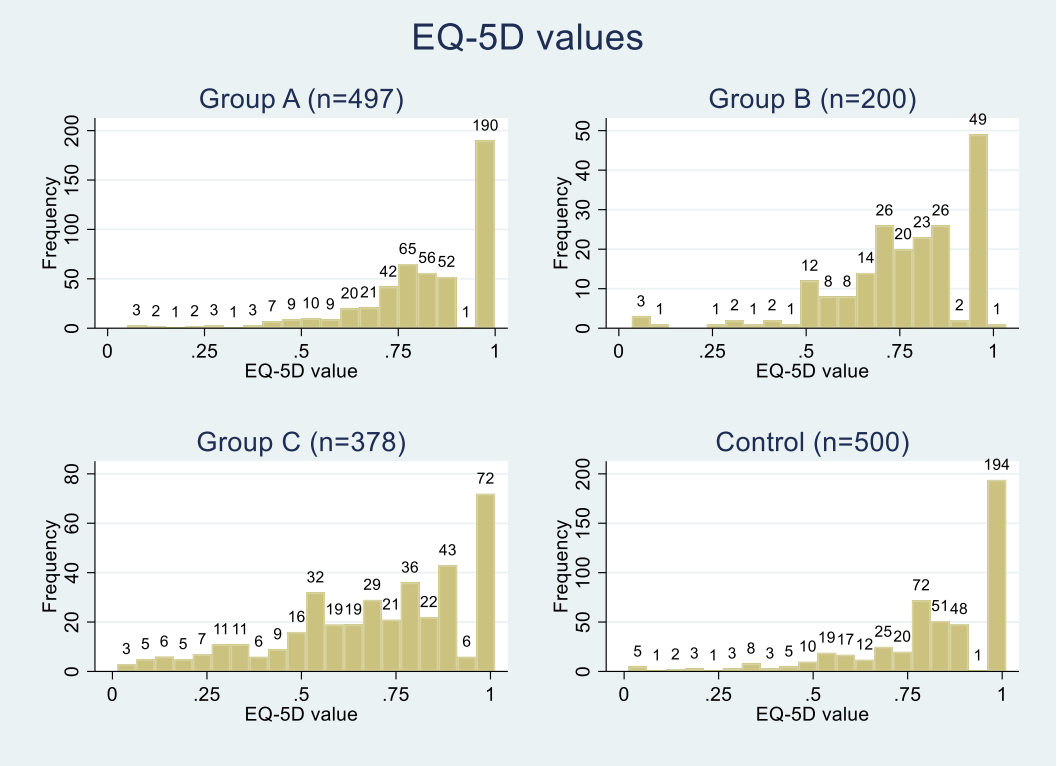
3.2 Quality of life and wellbeing in people that have experienced fertility problems

Figures 2-4 illustrate the distributions of the scores on each instrument. In most cases, the distribution of scores is negatively skewed, though this is more prominent in group A and the control group as there were relatively fewer low values/scores in these groups. Peaks at the upper end of the

scale are most evident for the EQ-5D values, and the FertiQoL Core scale generally has the broadest distribution of the four measures.

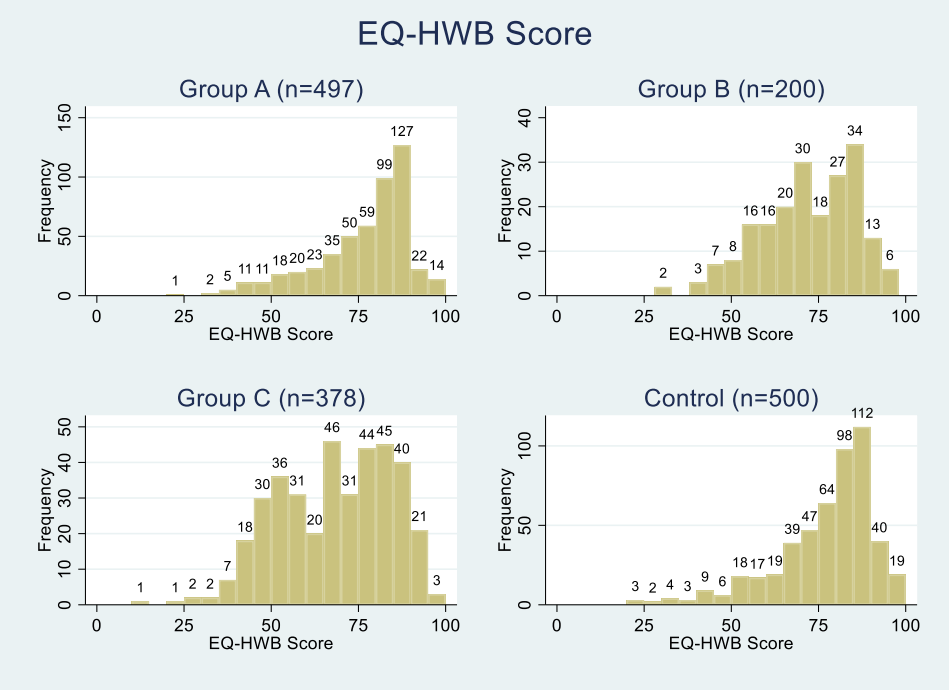
In all groups, most respondents had an EQ-5D value of greater than 0.5 (Figure 2). Group C had the largest proportion of respondents with EQ-5D values below 0.5. The distributions of EQ-HWB scores were similar between group A and the control group (negative skew), with more multimodal distributions in groups B and C (Figure 3). Overall, few respondents had normalised scores below 50 out of 100. However, the proportion of scores below 50 was far higher in group C relative to the other three groups. There was a relatively wide distribution of FertiQoL Core scores in each group (Figure 4). Whilst very few respondents had scores below 50 in group A, around 40% of respondents in groups B and C had scores below 50.

FIGURE 2. DISTRIBUTION OF EQ-5D VALUES, BY GROUP



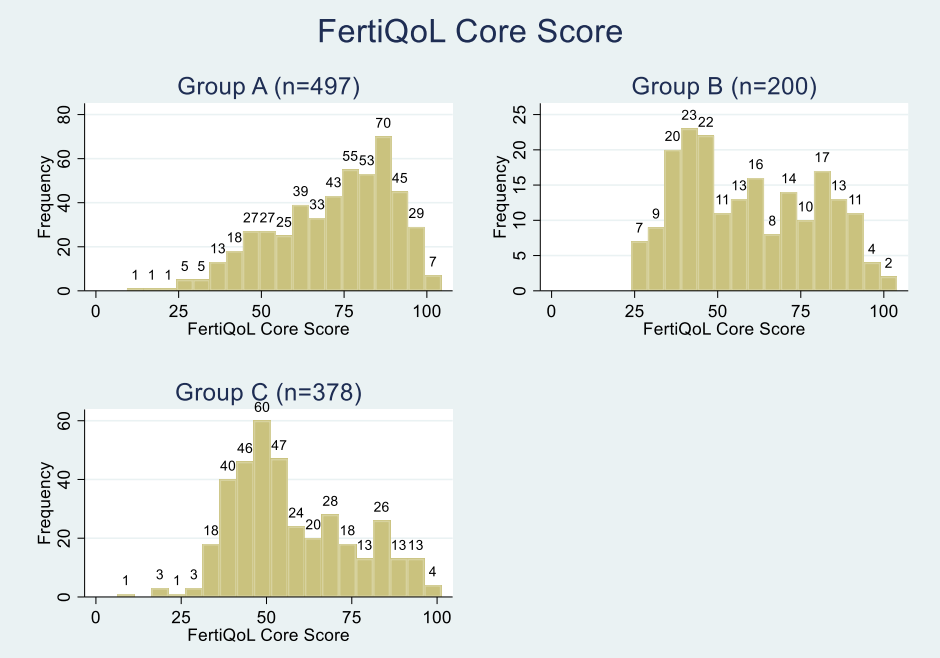
Group A: no/suboptimal treatment, did not have baby; group B: had treatment, did not have a baby; group C: had treatment had a baby; control: no fertility problems.Higher values indicate better HRQoL.

FIGURE 3. DISTRIBUTION OF EQ-HWB SCORES, BY GROUP



Group A: no/suboptimal treatment, did not have baby; group B: had treatment, did not have a baby; group C: had treatment had a baby; control: no fertility problems. Higher scores indicate better HRQoL.

FIGURE 4. DISTRIBUTION OF FERTIQOL CORE SCORES, BY GROUP

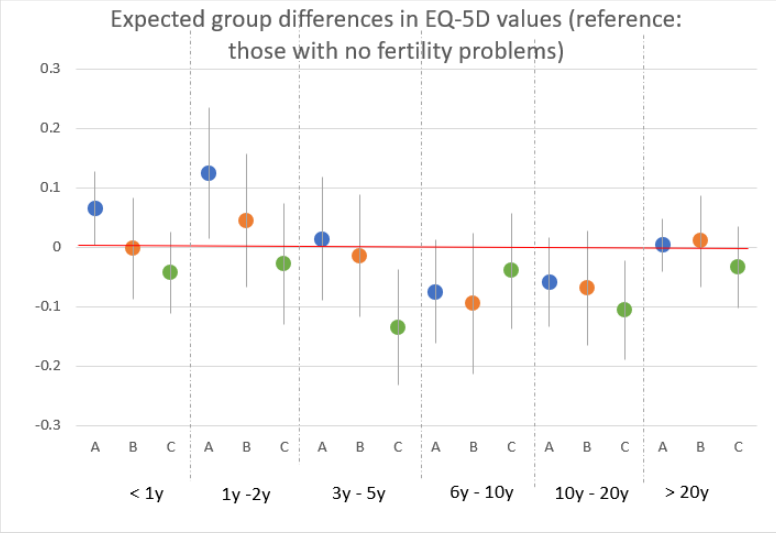


Group A: no/suboptimal treatment, did not have baby; group B: had treatment, did not have a baby; group C: had treatment had a baby; control: no fertility problems. Higher scores indicate better HRQoL.

Figures 5-7 show the expected inter-group differences in the PRO scores, split by group (A, B, C, and control) and by the time since respondents' most recent pregnancy attempt (in years). The estimates are obtained from OLS regressions controlling for sex, if partner, if dependent children at the time of the last pregnancy attempt, income, education, ethnic group, and LGBT+. (See detailed results in Table A4 and Table A5 in the Appendix).

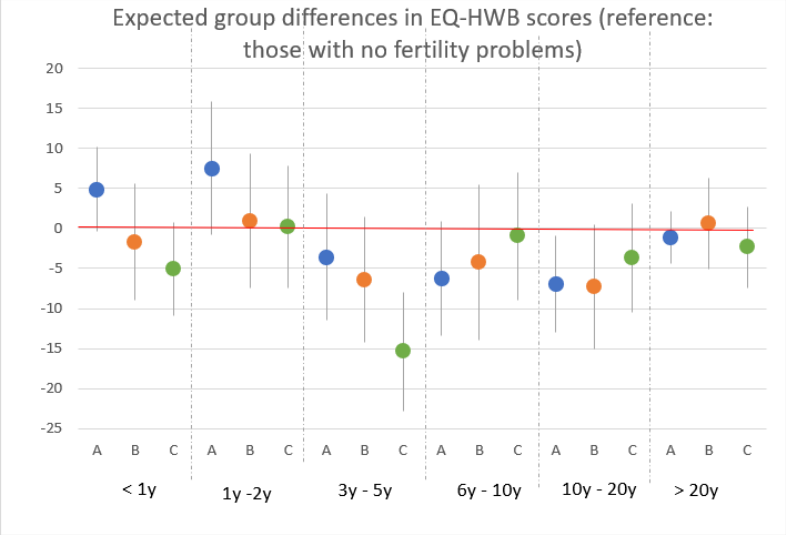
Contrary to our expectations, the mean scores suggest that those with fertility problems who went through a successful ART treatment have worse HRQoL (EQ-5D value) than those with fertility problems who did not use ARTs. This relation is stable across all the time segments (Figure 5). Those with a successful ART treatment also report worse HRQoL than those with children who did not have fertility problems. In the long run, assessments provide more similar scores for the three groups. A similar pattern was observed for EQ-HWB scores and FertiQoL Core scores among those who had their last pregnancy attempt up to five years ago (Figures 6 and 7). The relationship is reversed six years after the treatment, and those who had a successful ART treatment show slightly better QoL than those with fertility problems who did not use ARTs. This is more consistent with the previous literature on QoL. Thus EQ-HWB and FertiQoL scores seem to reflect better QoL in the long run.

FIGURE 5. MEAN EQ-5D VALUES BY GROUP AND TIME SINCE MOST RECENT PREGNANCY ATTEMPT



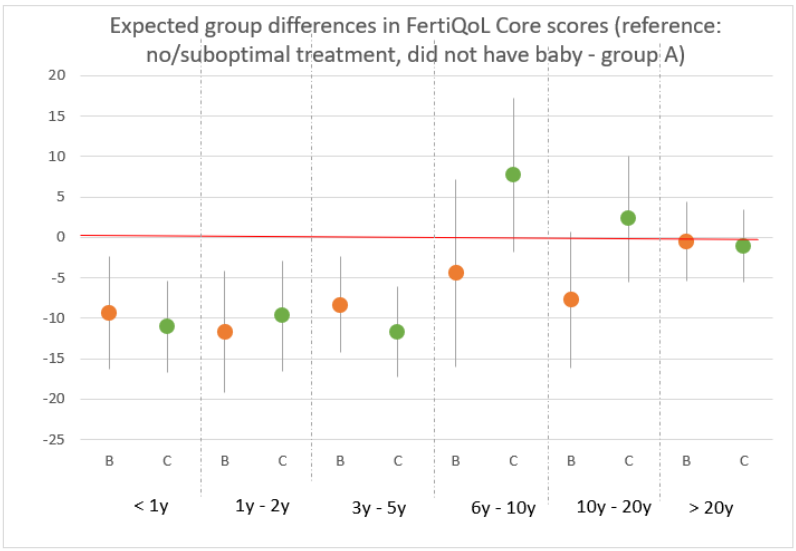
Group A: no/suboptimal treatment, did not have a baby; group B: had treatment, did not have a baby; group C: had treatment had a baby; control: no fertility problems. Higher values indicate better HRQoL.

FIGURE 6. MEAN EQ-HWB SCORE BY GROUP AND TIME SINCE MOST RECENT PREGNANCY ATTEMPT



Group A: no/suboptimal treatment, did not have a baby; group B: had treatment, did not have a baby; group C: had treatment had a baby; control: no fertility problems. Higher scores indicate better HRQoL

FIGURE 7. MEAN FERTIQOL CORE SCORE BY GROUP AND TIME SINCE MOST RECENT PREGNANCY ATTEMPT



Group A: no/suboptimal treatment, did not have baby; group B: had treatment, did not have a baby; group C: had treatment had a baby; control: no fertility problems. Higher scores indicate better HRQoL.

Table 7 summarises the results obtained in this analysis and compares them with the previous literature review. Not having dependent children at the most recent pregnancy attempt has an overall negative impact on the HRQoL/SWB scores, albeit it is not significant in most scenarios (See Tables A4 and A5 in the Appendix). Nonetheless, we have not considered B+ and B- separate groups in our analysis due to sample size constraints.

TABLE 7: COMPARISON OF OUR RESULTS WITH PREVIOUS RESULTS FROM THE PSYCHOLOGY LITERATURE

			Psychology literature review				Our results	
	Time label	Time description	Ref.	Who	What is measured (measure)	Results (group comparison)	Results (group comparison)	What is measured (measure)
Post-treatment short run	4	Immediately after treatment- up to 1 year	22	W	Anxiety (STAI), Depression (BDI-PC)	(B-, B+) < C	C < (B, control) < A	Utility (EQ-5D value), EQ-HWB score
			22	M	Anxiety (STAI), Depression (BDI-PC)	(B-, B+) = C	(C, B) < control	FertiQol score
			23	W	Anxiety (STAI), Depression (BDI)	C = control		
	5	1-2 years after ART	20	W	Life satisfaction	B- = B+ < C	C < control < B < A	Utility (EQ-5D value)
							(C, B) < control	FertiQol score
							(C, control, B) < A	EQ-HWB score
	6	3-5 years after ART	20	W	Life satisfaction	B- < B+ = C	C < (control, B, A)	Utility (EQ-5D value)
			17	W	Mental health (GHQ-12)	(B- , B+) = C	C < B < A < control	EQ-HWB score
			17	W	Life satisfaction (SWLS)	(B- , B+) < C	C < B < control	FertiQol score
			25	All	Anxiety (PGWB)	B- < control < C		
			25	All	Depression (PGWB)	B- < control = C		
			25	All	General Wellbeing (PGWB)	B- < control = C		
Post-treatment long-run	7	6-10 years after ART	20	W	Life satisfaction	B- = B+ = C	(C, B, A) < control	Utility (EQ-5D value)
			24	All	General Wellbeing (PGWB)	B- < B+ = C = control	(B, A) < C < control	EQ-HWB score
							B < control < C	FertiQol score
	8	11-20 years after ART	16	W	Mental health (MHI-5)	B- < (B+, C)	C < (B, A, control)	Utility (EQ-5D value), EQ-HWB score
			21	All	Self-esteem	B- < C	B < control < C	FertiQol score
			21	All	Occupational satisfaction	C < B-		
			21	All	Life satisfaction	B- = C		
	9	More than 20 years after ART					C < (B, A, control)	Utility (EQ-5D value)
							(C, B, A, control)	EQ-HWB score, FertiQol score

M: Men; W: women; All: couples. <: worse than; >: better than; =: similar to; ART: Artificial reproduction techniques; HRQoL: Health-related quality of life; SF-36: 36-item Short-Form Health Survey Questionnaire; MHI-5: five-item Mental Health Inventory (part of the SF-36); SIP: Sickness Impact Profile; HSCL: Hopkins Symptom Checklist; STAI: State and Trait Anxiety Inventory; BDI-PC: Beck Depression Inventory for Primary Care; SWLS: Satisfaction With Life Scale; GHQ-12: General health Questionnaire; PGWB: Psychological general wellbeing; A: infertile/subfertile, no access to treatment, no children; B-: infertile/subfertile, unsuccessful treatment, no children; ; B+: infertile/subfertile, unsuccessful treatment, children; C: infertile/subfertile, successful treatment. Control: fertile.

Table 8 provides a correlation matrix between the three PRO instruments. The highest correlation is between the EQ-5D value and EQ-HWB score (0.66), which can be classified as a moderate-strong correlation. The other correlations can also be classified as moderate (≥0.3). The most highly correlated generic PRO instrument with FertiQoL is the EQ-HWB (0.52), followed by EQ-5D-5L (0.39).

TABLE 8. CORRELATIONS BETWEEN THE PRO INSTRUMENTS

	EQ-5D	EQ-HWB	FertiQoL Core
EQ-5D	1.0000		
EQ-HWB	0.6556	1.0000	
FertiQol Core	0.3883	0.5232	1.0000

Correlations between the specific items on each instrument can be found in the Appendix. Overall, as expected based on the correlations between overall scores, there were generally larger correlations between items on EQ-HWB and FertiQoL (Table A3) compared with EQ-5D-5L and FertiQoL (Table A2).

4. Discussion

This study had two main aims: 1) to estimate health state utilities over time for different groups of individuals with varying experiences of fertility problems and fertility treatment; and, 2) to assess the performance of two generic PRO instruments (EQ-5D and EQ-HWB) in this context. Whilst all the data have been collected, there is one significant limitation. Due to the COVID-19 pandemic, the value set for the EQ-HWB instrument had not yet been produced. Therefore, we could not estimate values for the EQ-HWB to compare them to the EQ-5D. Nonetheless, we have been able to conduct analysis to address the two aims of the study, which this discussion section summarises.

An examination of the mean scores from the PRO instruments indicated that there were statistically significant differences in scores between the four groups recruited in this study in relation to EQ-5D values, EQ-HWB scores, and FertiQoL Core scores. However, these differences did not align with our *a priori* expectations that HRQoL would be higher for those that received treatment and even higher for those that had successful treatment (with the control group highest, or equivalent to group C). Instead, the mean scores suggest that the HRQoL in group A (no/suboptimal treatment, did not have a baby) was roughly the same as the control group (no fertility problems). Group B (had treatment, did not have a baby) had worse HRQoL compared with these groups, and group C (had treatment, had a baby) had even worse HRQoL. A similar pattern was observed with EQ-HWB scores. Furthermore, FertiQoL Core scores were highest in group A, followed by group B, followed by group C.

A closer examination of the data pointed towards some potential explanations for this. Firstly, there were substantial differences in the characteristics of participants in each of the four groups recruited to this study. For example, respondents in groups A and the control group were older on average, and these groups had a much higher proportion of male respondents than the other groups. The average group scores have been adjusted by age and sex, as well as for a number of additional socioeconomic and demographic characteristics. However, we cannot rule out the existence of confounding factors that could have biased the results. The methodological challenges around suitable control groups and comparing the experience of different fertility groups has been also present in the psychology literature.[34]

Secondly, it was found that the time since the respondents' most recent pregnancy attempt appeared to have a significant impact on values/scores (lower HRQoL was observed in those with more recent pregnancy attempts), and the proportions of individuals in each category varied by group. For

example, 42% of the control group most recently attempted to get pregnant over 20 years ago, compared with 9% of group C. For those that were successful in their attempts, the time since the most recent pregnancy attempt variable indicates those that have young children, which is relevant given that the study was conducted during a national lockdown because of the COVID-19 pandemic. In other words, we might expect a lower quality of life in those that had recent successful pregnancy attempts (group C and the control group) due to the pandemic as lockdown restrictions likely meant that new parents could not have the full experience of parenthood they envisioned. Few people had recent pregnancy attempts in the control group relative to group C, which may have partly explained the unexpected pattern in mean values between groups.

It is unclear why HRQoL may be worse for individuals who received ART treatment than those who did not. There may be selection bias occurring whereby individuals who received ART treatment and responded to this survey systematically differed from those who had not undertaken ART treatment. Again, whilst we controlled for several factors in our regression analysis, there may be other factors driving this result for which we did not collect data. Additionally, HRQoL measures may capture well the physical burden of receiving ART (and the burden of pregnancy and childcare, if successful), but fail to capture other relevant dimensions for the fertility journey, such as life satisfaction, feeling that life is worthwhile, and the kind related to happiness and wellbeing. If parenthood (or lack thereof) impacts the quality of life of those receiving ART in dimensions that go beyond 'health', then it is reasonable to think that HRQoL measures fail to capture the whole effect.

Comparisons of the performance of the measures indicated that the inclusion of subjective wellbeing items could identify differences better aligned with our hypothesis based on the psychology literature. For instance, the EQ-5D keeps a similar pattern across the time points, with those who had a successful ART (group C) reporting lower values than the other groups A, B, and control. However, FertiQoL and EQ-HWB scores suggest an order reversal (group C better than group A and B) from six or more years since the last pregnancy attempt, keeping the convergence in scores from more than 20 years since the last pregnancy attempt. Whilst the differences in the performance of the EQ-5D and EQ-HWB were not overwhelming, the broader focus of the EQ-HWB items and better correlation with FertiQoL suggests that this may be a relatively better measure to use in the context of fertility-related QoL. However, it is essential to note that the use of value sets to obtain utilities could significantly impact the results of a head-to-head comparison of this nature. The value set for the EQ-HWB will not be based upon all 25 items; therefore, some of the sensitivity will be lost when converting the questionnaire responses to utilities. Furthermore, value sets introduce noise into the data because they are based on a preference elicitation exercise from a separate sample. Therefore, it would be useful to make these comparisons again once a value set becomes available for EQ-HWB.

HRQoL measures provide a counter-intuitive result, implying that a desire for ART may be "irrational". Broader generic or condition-specific measures of HRQoL (such as EQ-HWB and FertiQoL, respectively), which add wellbeing dimensions to the outcome description, show a better correspondence with the evidence observed in the psychology literature. However, even these results do not align with our *a priori* expectations or results from the psychology literature regarding the relative ordering of the groups in our study by quality-of-life. Future research should seek to elucidate whether a 'health-related' societal measure of QoL which also includes aspects of wellbeing could more meaningfully capture the full effects of infertility and fertility treatment. In the absence of such a measure, relevant and important dimensions of the impact of infertility on the individual are undervalued or disregarded entirely. Further comparisons would be beneficial when a value set for EQ-HWB becomes available to test the robustness of this conclusion. In the case that generic health and wellbeing measures such as EQ-HWB are still insensitive to the full impacts of infertility, an alternative approach (such as using a vignette to describe the condition for a posterior time trade-off task or adding an explicit bolt-on around infertility to existing measures) may be the most appropriate way forward.

5. Conclusion

The results suggest that HRQoL differed on average between individuals in the four groups recruited to take part in this study. Notably, individuals that received ART treatment and had a successful pregnancy had worse HRQoL on average, compared with the other groups. There is some evidence to suggest that EQ-HWB may be superior to EQ-5D in capturing HRQoL in this context. Including wellbeing items that go beyond health is likely to explain the better alignment of EQ-HWB figures with the evidence provided by the psychology literature on the effects of infertility in the short and long run. Further analysis is required in order to understand how to appropriately conceptualise and measure the value of ART.

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Appendix

TABLE A1. CORRELATIONS BETWEEN EQ-5D-5L AND EQ-HWB ITEMS

EQ-HWB Items		EQ-5D-5L Dimensions				
		Mobility	Self-Care	Usual Activities	Pain/ Discomfort	Anxiety/ Depression
1	Difficult to See	0.28	0.26	0.34	0.29	0.32
2	Difficult to Hear	0.33	0.38	0.35	0.26	0.27
3	Difficult to Get Around	0.54	0.47	0.52	0.41	0.30
4	Difficult to do Day-to-Day Activities	0.53	0.49	0.55	0.37	0.33
5	Difficult to do Self-Care	0.47	0.51	0.48	0.37	0.32
6	No Control	0.30	0.30	0.35	0.29	0.34
7	Unable to Cope	0.35	0.40	0.40	0.31	0.47
8	Trouble Remembering	0.30	0.33	0.34	0.30	0.35
9	Trouble Concentrating	0.26	0.32	0.30	0.27	0.41
10	Felt Anxious	0.23	0.22	0.29	0.31	0.59
11	Felt Frustrated	0.26	0.24	0.31	0.30	0.53
12	Felt Sad/Depressed	0.25	0.27	0.27	0.26	0.57
13	Felt Nothing to Look Forward to	0.20	0.29	0.29	0.24	0.53
14	Felt Lonely	0.25	0.28	0.32	0.24	0.48
15	Felt Unsupported	0.23	0.31	0.30	0.23	0.48
16	Felt Unsafe	0.28	0.38	0.31	0.28	0.34
17	Sleep Problems	0.24	0.20	0.27	0.32	0.42
18	Felt Exhausted	0.27	0.27	0.32	0.30	0.46
19	Felt Accepted	-0.15	-0.18	-0.16	-0.10	-0.29
20	Felt Good About Myself	-0.10	-0.13	-0.15	-0.15	-0.40
21	Able to do the Things I Wanted to do	-0.18	-0.18	-0.25	-0.17	-0.35
22	Had Physical Pain	0.43	0.38	0.42	0.57	0.30
23	Pain in Last 7 Days	0.50	0.43	0.49	0.66	0.41
24	Had Physical Discomfort	0.44	0.43	0.44	0.43	0.38
25	Physical Discomfort in Last 7 Days	0.51	0.45	0.49	0.57	0.47

Pink cells indicate a weak correlation; yellow cells indicate a moderate correlation.

TABLE A2. CORRELATIONS BETWEEN EQ-5D-5L AND FERTIQOL ITEMS

FertiQoL Items		EQ-5D-5L Dimensions				
		Mobility	Self-Care	Usual Activities	Pain/ Discomfort	Anxiety/ Depression
1	Attention/Concentration Impaired	-0.20	-0.30	-0.23	-0.19	-0.35
2	Cannot Move Ahead with Goals/Plans	-0.19	-0.26	-0.21	-0.17	-0.31
3	Feel Drained/Worn Out	-0.19	-0.27	-0.20	-0.19	-0.33
4	Able to Cope	0.02	-0.01	0.01	0.01	0.07
5	Satisfied with Support from Friends	-0.01	-0.03	-0.07	-0.05	-0.20
6	Satisfied with Sexual Relationship	0.01	0.01	-0.02	-0.03	-0.19
7	Causing Jealousy/Resentment	-0.18	-0.26	-0.21	-0.16	-0.34
8	Experience Grief/Feelings of Loss	-0.18	-0.24	-0.23	-0.23	-0.36
9	Fluctuating Between Hope/Despair	-0.17	-0.23	-0.18	-0.19	-0.35
10	Socially Isolated	-0.25	-0.34	-0.29	-0.22	-0.36
11	Affectionate with Partner	0.01	0.05	0.03	-0.04	0.05
12	Interference with Work/Obligations	-0.21	-0.30	-0.22	-0.19	-0.30
13	Uncomfortable in Social Situations	-0.18	-0.26	-0.22	-0.20	-0.30
14	Family Understanding	-0.02	-0.04	-0.02	-0.03	0.03
15	Strengthened Commitment to Partner	0.03	0.03	0.01	-0.01	0.10
16	Sad/Depressed	-0.17	-0.25	-0.21	-0.19	-0.39
17	Inferior to People with Children	-0.23	-0.32	-0.25	-0.21	-0.34
18	Fatigued	-0.23	-0.28	-0.26	-0.23	-0.38
19	Negative Impact on Relationship	-0.23	-0.32	-0.26	-0.19	-0.34
20	Difficult to Talk to Partner	-0.21	-0.27	-0.21	-0.16	-0.33
21	Content with Relationship	0.03	0.04	0.04	0.01	0.05
22	Social Pressure	-0.20	-0.28	-0.21	-0.19	-0.31
23	Angry	-0.20	-0.26	-0.24	-0.20	-0.35
24	Pain/Discomfort	-0.28	-0.35	-0.30	-0.25	-0.35

FertiQoL rating scales excluded, as these did not form part of the FertiQoL Core score. Pink cells indicate a weak correlation; yellow cells indicate a moderate correlation

TABLE A3. CORRELATIONS BETWEEN EQ-HWB AND FERTIQOL ITEMS

FertiQoL Items		EQ-HWB Items																								
		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
1	Attention/Concentration Impaired	-0.26	-0.21	-0.27	-0.29	-0.28	-0.39	-0.48	-0.34	-0.43	-0.40	-0.40	-0.41	-0.40	-0.48	-0.46	-0.49	-0.30	-0.40	0.36	0.24	0.28	-0.30	-0.23	-0.41	-0.29
2	Cannot Move Ahead with Goals/Plans	-0.22	-0.18	-0.25	-0.28	-0.27	-0.37	-0.45	-0.32	-0.39	-0.37	-0.37	-0.39	-0.37	-0.42	-0.42	-0.46	-0.29	-0.39	0.32	0.24	0.26	-0.31	-0.22	-0.37	-0.27
3	Feel Drained/Worn Out	-0.24	-0.20	-0.27	-0.27	-0.28	-0.38	-0.48	-0.35	-0.41	-0.39	-0.38	-0.41	-0.40	-0.46	-0.45	-0.49	-0.30	-0.41	0.37	0.24	0.28	-0.31	-0.23	-0.39	-0.27
4	Able to Cope	0.00	-0.02	-0.01	0.02	0.00	-0.01	-0.01	-0.03	-0.03	0.07	0.03	0.04	0.05	0.04	0.05	-0.05	0.03	0.04	-0.14	-0.17	-0.16	-0.03	0.01	-0.03	0.01
5	Satisfied with Support from Friends	-0.06	-0.02	-0.05	-0.08	-0.07	-0.08	-0.13	-0.07	-0.12	-0.19	-0.17	-0.17	-0.20	-0.18	-0.24	-0.11	-0.13	-0.22	0.21	0.28	0.24	-0.10	-0.13	-0.06	-0.12
6	Satisfied with Sexual Relationship	-0.06	0.03	0.00	-0.04	-0.01	-0.06	-0.09	-0.04	-0.10	-0.16	-0.16	-0.18	-0.21	-0.16	-0.17	-0.09	-0.10	-0.17	0.21	0.27	0.20	-0.05	-0.09	-0.03	-0.07
7	Causing Jealousy/Resentment	-0.19	-0.16	-0.23	-0.24	-0.21	-0.26	-0.38	-0.28	-0.34	-0.38	-0.33	-0.40	-0.36	-0.37	-0.39	-0.36	-0.29	-0.36	0.35	0.32	0.34	-0.23	-0.20	-0.28	-0.25
8	Experience Grief/Feelings of Loss	-0.23	-0.17	-0.22	-0.24	-0.24	-0.33	-0.41	-0.30	-0.38	-0.42	-0.37	-0.39	-0.37	-0.42	-0.43	-0.37	-0.34	-0.42	0.29	0.27	0.28	-0.32	-0.27	-0.34	-0.27
9	Fluctuating Between Hope/Despair	-0.21	-0.15	-0.20	-0.24	-0.23	-0.33	-0.41	-0.32	-0.38	-0.40	-0.36	-0.42	-0.41	-0.44	-0.45	-0.41	-0.33	-0.40	0.33	0.27	0.29	-0.29	-0.23	-0.34	-0.28
10	Socially Isolated	-0.29	-0.28	-0.32	-0.33	-0.33	-0.35	-0.48	-0.37	-0.40	-0.41	-0.38	-0.42	-0.43	-0.48	-0.49	-0.48	-0.31	-0.43	0.35	0.30	0.32	-0.33	-0.24	-0.38	-0.32
11	Affectionate with Partner	0.06	0.05	0.05	0.07	0.08	0.05	0.07	0.06	0.06	0.05	0.03	0.06	0.09	0.12	0.09	0.02	0.00	0.05	-0.16	-0.15	-0.12	-0.02	-0.04	0.02	-0.01
12	Interference with Work/Obligations	-0.25	-0.26	-0.28	-0.26	-0.30	-0.37	-0.44	-0.38	-0.39	-0.33	-0.32	-0.36	-0.36	-0.43	-0.43	-0.49	-0.26	-0.34	0.34	0.22	0.25	-0.28	-0.21	-0.38	-0.26
13	Uncomfortable in Social Situations	-0.24	-0.23	-0.27	-0.26	-0.30	-0.32	-0.40	-0.35	-0.34	-0.34	-0.33	-0.37	-0.33	-0.42	-0.44	-0.45	-0.26	-0.34	0.33	0.26	0.28	-0.25	-0.19	-0.34	-0.24
14	Family Understanding	-0.01	-0.02	0.00	0.02	-0.01	0.03	0.00	-0.03	-0.02	0.04	0.05	0.04	0.05	0.04	0.07	-0.11	0.02	0.06	-0.12	-0.21	-0.19	0.02	-0.01	-0.05	-0.02
15	Strengthened Commitment to Partner	0.01	0.05	0.04	0.05	0.07	0.04	0.04	0.03	0.03	0.05	0.06	0.06	0.12	0.07	0.08	-0.03	0.06	0.06	-0.13	-0.21	-0.16	-0.02	-0.01	0.01	0.04
16	Sad/Depressed	-0.21	-0.14	-0.24	-0.26	-0.21	-0.29	-0.44	-0.31	-0.36	-0.41	-0.38	-0.43	-0.42	-0.47	-0.45	-0.39	-0.33	-0.40	0.35	0.29	0.32	-0.30	-0.26	-0.35	-0.28
17	Inferior to People with Children	-0.22	-0.21	-0.28	-0.29	-0.29	-0.35	-0.46	-0.33	-0.36	-0.40	-0.38	-0.41	-0.40	-0.46	-0.46	-0.42	-0.31	-0.40	0.38	0.30	0.34	-0.32	-0.24	-0.38	-0.29
18	Fatigued	-0.27	-0.24	-0.28	-0.29	-0.30	-0.37	-0.48	-0.37	-0.42	-0.43	-0.39	-0.41	-0.41	-0.48	-0.48	-0.49	-0.31	-0.44	0.37	0.29	0.32	-0.33	-0.25	-0.41	-0.34
19	Negative Impact on Relationship	-0.26	-0.23	-0.27	-0.26	-0.27	-0.33	-0.42	-0.34	-0.39	-0.39	-0.37	-0.38	-0.39	-0.46	-0.46	-0.48	-0.29	-0.39	0.35	0.28	0.30	-0.29	-0.23	-0.35	-0.30
20	Difficult to Talk to Partner	-0.20	-0.19	-0.23	-0.26	-0.23	-0.30	-0.40	-0.31	-0.38	-0.36	-0.37	-0.36	-0.37	-0.45	-0.42	-0.42	-0.29	-0.40	0.33	0.27	0.30	-0.24	-0.18	-0.35	-0.24
21	Content with Relationship	0.09	0.08	0.05	0.08	0.09	0.08	0.10	0.05	0.06	0.07	0.06	0.07	0.11	0.09	0.09	0.04	0.01	0.09	-0.23	-0.18	-0.17	0.02	0.01	0.02	0.03
22	Social Pressure	-0.18	-0.16	-0.22	-0.21	-0.20	-0.28	-0.37	-0.26	-0.31	-0.32	-0.31	-0.31	-0.31	-0.36	-0.38	-0.34	-0.24	-0.35	0.31	0.24	0.26	-0.25	-0.21	-0.32	-0.24
23	Angry	-0.20	-0.18	-0.25	-0.25	-0.23	-0.34	-0.44	-0.32	-0.35	-0.37	-0.38	-0.42	-0.40	-0.44	-0.45	-0.40	-0.32	-0.41	0.34	0.28	0.31	-0.30	-0.24	-0.37	-0.28
24	Pain/Discomfort	-0.29	-0.28	-0.33	-0.36	-0.32	-0.39	-0.49	-0.41	-0.45	-0.40	-0.38	-0.41	-0.41	-0.48	-0.46	-0.54	-0.33	-0.42	0.31	0.19	0.26	-0.37	-0.29	-0.45	-0.34

FertiQoL rating scales excluded, as these did not form part of the FertiQoL Core score. Pink cells indicate a weak correlation; yellow cells indicate a moderate correlation.

TABLE A4. ORDINARY LEAST SQUARE REGRESSIONS BY OUTCOME MEASURE AND TIME SINCE LAST PREGNANCY ATTEMPT

	Less than a year			From 1 to 2 years			From 3 to 5 years		
	EQ-5D	EQ-HWB	FertiQoL	EQ-5D	EQ-HWB	FertiQoL	EQ-5D	EQ-HWB	FertiQoL
Cont: Age (years)	0.001	0.237*	0.455***	-0.002	0.329*	0.235	0.001	0.523***	0.701***
	(0.001)	(0.124)	(0.147)	(0.002)	(0.172)	(0.178)	(0.002)	(0.159)	(0.144)
Dummy: Male	0.017	-0.898	1.528	0.047	0.161	3.479	-0.021	-4.672*	-0.524
	(0.024)	(2.048)	(2.478)	(0.035)	(2.645)	(2.755)	(0.034)	(2.595)	(2.508)
Dummy: In a relationship	-0.013	2.464	-1.307	-0.060	-3.336	-12.365	0.103**	11.050***	4.645
	(0.046)	(3.983)	(4.659)	(0.086)	(6.415)	(10.228)	(0.044)	(3.325)	(3.088)
Dummy: Heterosexual	0.143***	8.227*	-2.277	0.021	-4.866	0.686	-0.006	-5.929	-2.866
	(0.051)	(4.418)	(5.752)	(0.070)	(5.279)	(6.056)	(0.089)	(6.760)	(5.762)
Dummy: Household income >£40,000	0.003	0.675	-3.743	-0.099**	-4.444	-3.560	0.036	2.427	6.401**
	(0.026)	(2.238)	(2.788)	(0.041)	(3.037)	(3.413)	(0.038)	(2.928)	(2.994)
Dummy: Higher education[1]	0.022	0.261	-0.114	0.035	5.339**	-4.623	-0.033	-4.117	-8.979***
	(0.024)	(2.102)	(2.562)	(0.035)	(2.639)	(2.802)	(0.033)	(2.541)	(2.469)
Dummy: White	0.043	3.576	-0.310	0.085	-1.807	-1.399	0.041	0.586	-0.112
	(0.028)	(2.411)	(2.960)	(0.056)	(4.165)	(4.854)	(0.048)	(3.645)	(3.672)
Dummy: Group A	0.065**	4.887*		0.125**	7.551*		0.014	-3.556	
	(0.031)	(2.692)		(0.056)	(4.201)		(0.052)	(3.995)	
Dummy: Group B	-0.003	-1.701	-9.298***	0.045	0.904	-11.679***	-0.015	-6.431	-8.319***
	(0.043)	(3.690)	(3.524)	(0.057)	(4.262)	(3.782)	(0.052)	(3.970)	(3.022)
Dummy: Group C	-0.043	-5.111*	-11.051***	-0.028	0.185	-9.690***	-0.135***	-15.404***	-11.697***
	(0.035)	(2.975)	(2.844)	(0.052)	(3.881)	(3.472)	(0.049)	(3.741)	(2.820)
Dummy: No dep. children at most recent attempt	-0.003	-2.140	-5.252**	0.005	-2.243	-3.071	-0.077**	-2.254	-2.087
	(0.024)	(2.026)	(2.368)	(0.032)	(2.392)	(2.351)	(0.035)	(2.692)	(2.394)
Constant	0.574***	58.667***	57.458***	0.803***	65.505***	72.167***	0.706***	61.437***	37.928***
	(0.079)	(6.789)	(8.423)	(0.123)	(9.217)	(11.676)	(0.122)	(9.324)	(8.863)
Observations	323	323	258	221	221	180	255	255	208
R-squared	0.101	0.087	0.164	0.136	0.097	0.208	0.161	0.201	0.299
Adj. R-squared	0.0691	0.0551	0.130	0.0908	0.0500	0.162	0.123	0.164	0.264

*Cont: continuous variable; int: interaction variable; dummy: dummy variable. Standard errors in parentheses; *** p<0.01, ** p<0.05, * p<0.1. [1]Highest qualification was at 'higher education' level. Dep. = dependent. Group A: no/suboptimal treatment, did not have baby; group B: had treatment, did not have a baby; group C: had treatment had a baby; control: no fertility problems. Higher utilities/scores indicate better HRQoL*

TABLE A5. ORDINARY LEAST SQUARE REGRESSIONS BY OUTCOME MEASURE AND TIME SINCE LAST PREGNANCY ATTEMPT (CONT. OF TABLE A4)

	From 6 to 10 years			From 11 to 20 years			More than 20 years		
	EQ-5D	EQ-HWB	FertiQoL	EQ-5D	EQ-HWB	FertiQoL	EQ-5D	EQ-HWB	FertiQoL
Cont: Age (years)	-0.002 (0.002)	0.096 (0.162)	0.687*** (0.217)	-0.001 (0.002)	0.111 (0.155)	0.345 (0.231)	0.000 (0.001)	0.310*** (0.079)	0.190* (0.103)
Dummy: Male	0.070* (0.037)	6.262** (3.010)	7.106* (4.125)	0.037 (0.031)	1.891 (2.548)	6.849* (3.742)	0.036* (0.020)	1.871 (1.423)	2.989* (1.793)
Dummy: In a relationship	0.016 (0.054)	4.348 (4.472)	-12.679** (5.734)	0.043 (0.042)	7.033** (3.391)	4.990 (5.241)	0.021 (0.025)	4.030** (1.846)	-6.480*** (2.265)
Dummy: Heterosexual	0.008 (0.103)	6.626 (8.482)	-4.109 (9.587)	-0.105 (0.098)	-16.732** (7.979)	-4.522 (12.904)	-0.020 (0.074)	4.717 (5.421)	-0.314 (5.756)
Dummy: Household income >£40,000	0.022 (0.037)	-0.413 (3.004)	0.545 (4.241)	0.037 (0.031)	3.299 (2.541)	-1.019 (3.715)	0.045** (0.020)	4.559*** (1.470)	3.342* (1.760)
Dummy: Higher education[1]	0.032 (0.035)	3.684 (2.856)	0.835 (3.958)	-0.013 (0.031)	-1.449 (2.478)	-4.766 (3.514)	0.007 (0.019)	0.109 (1.411)	0.479 (1.715)
Dummy: White	-0.064 (0.048)	-2.184 (3.910)	-6.912 (5.717)	0.078 (0.049)	3.981 (3.994)	-2.757 (5.591)	0.081 (0.049)	7.897** (3.579)	0.630 (5.772)
Dummy: Group A	-0.074* (0.044)	-6.253* (3.598)		-0.059 (0.038)	-6.989** (3.055)		0.003 (0.023)	-1.099 (1.656)	
Dummy: Group B	-0.095 (0.060)	-4.212 (4.897)	-4.419 (5.827)	-0.069 (0.049)	-7.258* (3.931)	-7.718* (4.236)	0.010 (0.039)	0.624 (2.871)	-0.490 (2.501)
Dummy: Group C	-0.040 (0.049)	-0.957 (4.049)	7.735 (4.805)	-0.105** (0.042)	-3.692 (3.432)	2.302 (3.926)	-0.033 (0.035)	-2.344 (2.552)	-1.079 (2.259)
Dummy: No dep. children at most recent attempt	0.043 (0.035)	1.564 (2.907)	-4.675 (3.849)	-0.004 (0.031)	-0.898 (2.504)	3.348 (3.406)	0.005 (0.021)	0.479 (1.514)	-1.007 (1.983)
Constant	0.854*** (0.140)	64.474*** (11.536)	48.893*** (14.084)	0.951*** (0.137)	88.962*** (11.109)	52.158*** (19.301)	0.744*** (0.101)	55.839*** (7.384)	74.502*** (8.481)
Observations	151	151	105	187	187	118	371	371	186
R-squared	0.084	0.094	0.240	0.095	0.124	0.135	0.051	0.126	0.111
Adj. R-squared	0.0115	0.0223	0.159	0.0383	0.0685	0.0547	0.0223	0.0992	0.0600

*Cont: continuous variable; int: interaction variable; dummy: dummy variable. Standard errors in parentheses; *** p<0.01, ** p<0.05, * p<0.1. [1]Highest qualification was at 'higher education' level. Dep. = dependent. Group A: no/suboptimal treatment, did not have baby; group B: had treatment, did not have a baby; group C: had treatment had a baby; control: no fertility problems. Higher utilities/scores indicate better HRQoL*

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