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# Valuing infertility treatment: Why QALYs are inadequate, and an alternative approach to cost-effectiveness thresholds

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## Introduction

The ability to reproduce is the most fundamental of all human activities, and thus the inability to do so (infertility) is acknowledged as a disease by key international bodies such as the World Health Organization and the United Nations (1). Infertility is an increasingly prevalent global health issue with >180 million people affected (2), with a similar prevalence among high- and low-income countries (3). The trend to later childbearing, increasing rates of obesity and some sexually transmitted infections, and the well-documented decline in sperm counts worldwide are largely responsible (4–6). While infertility is not a life-threatening disease, it can cause significant long-term psychological suffering, stigmatization, and violence towards women (2, 7).

Medically assisted infertility treatments allow many affected individuals to have children. More traditional forms of infertility treatment, such as ovulation induction and artificial insemination, are still widely used. However, the treatment of infertility has been revolutionized over the last forty years with the advent of assisted reproductive technologies (ART), such as *in vitro* fertilization (IVF) where fertilization of a woman's eggs occurs in a laboratory and the resulting embryo(s) is transferred into the uterus. Up to 9% of children in some countries are now conceived using ARTs (8), with >2 million ART treatment cycles performed each year (9).

Infertility treatment is expensive, particularly ARTs (~US$12,000/cycle), with women often needing many cycles to achieve pregnancy, if at all. The value of the global infertility treatment market is estimated to reach US$27 billion by 2026 (10), representing a significant economic burden to healthcare systems, governments, third-party insurers, and patients.

There is arguably no other medical treatment that exhibits such varying arrangements for funding by governments and third parties as ART. In the latest global survey of ART practices and policies undertaken by the International Federation of Fertility Societies, fewer than half of the 85 countries surveyed reported any type of financial support for ART treatment, and only 17 offered full reimbursement (11). If funded, most programs use eligibility criteria (e.g., age, marital status) and apply limits on the number of treatment cycles financed (12–20). The consequence of this is unequal and inequitable access to ARTs, with a significant reliance on out-of-pocket funding (21).

Arguably, one of the key reasons for such variation in funding arrangements is the inadequacy of traditional health technology assessment (HTA) methods to capture the "value" of infertility treatments. Indeed, the most appropriate method for capturing the value of future parenthood has long been a challenge for economists (22). Typically, a cost-utility analysis (CUA) - which is the mainstay of HTA methods - reports outcomes in terms of additional cost per quality-adjusted life-year (QALY). The QALY is a composite measure that captures health-related quality of life (HRQoL) and life expectancy, the aim of which is to generate a single metric that allows direct comparisons of benefit across dissimilar health interventions.

However, as we will argue here, QALYs are not well suited to reflect the value associated with a new life generated using infertility treatment, and thus do not adequately inform decision-makers regarding the opportunity cost of allocating healthcare funds to ARTs compared to alternate health services. Instead, we argue that, in the absence of accepted preference-based utility instruments that go beyond HRQoL, the use of cost-effectiveness/willingness-to-pay (WTP) values for the birth of a baby within a cost-benefit analysis (CBA) framework is more appropriate for assessing value for money of infertility treatment.

## How are infertility treatments evaluated economically

Because of the challenges associated with QALYs in the context of infertility treatment, the majority of cost-effectiveness analyses use clinical outcome metrics such as live births or pregnancies and report incremental cost-effectiveness ratios based on the additional cost incurred to achieve an additional live birth or pregnancy (23–62). While such studies allow conclusions about the comparative cost-effectiveness within the narrow scope of infertility treatment, the WTP threshold for a child created through infertility treatments is unknown and thus it is unclear whether a treatment represents good value for money.

Using QALYs to measure the utility of infertility treatment outcomes within a CUA framework is uncommon and inconsistently applied (63). Some studies have considered QALYs of the mother (64), some of both parents (65, 66), and some of the children born through infertility treatment (67). While the use of QALYs to measure outcomes is conceptually appealing there are several issues in the context of infertility treatment that limit their applicability.

## QALYs: Creation of new life vs. changes in HRQoL of existing lives

Infertility treatment is a medical intervention to treat a disease. However, it is unique because unlike most medical interventions which are assessed based on their ability to improve, extend, or save an existing life, infertility treatment is judged based on its ability to create a new life. As argued by Devlin (68), QALYs were designed to capture improvements in patients, not to value new life. Utility weights, which reflect individuals' preferences for specific health states, only exist for health states of an existing life (69–71). Simply applying lifetime QALYs to a new life for use in a CUA is not appropriate because additional lives are not improvements in health and preventing someone's death is not the same as creating their life. It is not possible to improve the quality of life of someone who has not been conceived by conceiving them (68).

In line with this argument, Luyten (72) recently proposed guidelines for inclusion of QALYs for health interventions that affect future lives, including contraception, abortion, disease screening and infertility treatment. According to these guidelines, QALYs of future lives should only be included if these lives would exist independent of the treatment choice. Since the creation of life in the context of infertility treatment is only possible for women who choose to undergo infertility treatment, QALYs of these future lives should not be considered in HTA of infertility treatment. While it can be perceived as inconsistent that QALYs are a valid metric for assessing perinatal interventions (e.g., perinatal screening to avoid disease) (73–75) but are not adequate for assessing infertility treatment, it is important to differentiate the timing and objective of the decision/choice to undergo the intervention when evaluating it. In the case of perinatal interventions and screening, the child is "necessary/assumed" for the healthcare service, and thus health impacts for that child should be counted. In contrast, infertility treatment and other reproductive interventions affect the "potential" to have a child and thus health impacts should not be counted.

Furthermore, to be consistent, the application of QALYs would need to be equally applied to interventions that increase fertility (e.g., infertility treatment) and those that reduce fertility (e.g., contraception). If arguing that the number of QALYs a child born through infertility treatment would experience should be included in economic evaluations, then the number of QALYs lost due to preventing the birth of a child should also be considered (72). Such an approach to valuing potential life is conceptually flawed, ethically problematic, and has not been adopted within a HTA framework (63).

## Parenthood impacts quality of life domains beyond health

Certainly, there is scope to use QALYs to value the reduction in psychological distress in would-be parents by creating a new life using infertility treatment. However, infertile couples who resolve their childlessness report high levels of life satisfaction and self-esteem, but not depressive symptoms, the latter of which are more likely to be captured by the domains included in common QALY instruments such as the EQ-5D (76–78).

While QALYs capture changes in HRQoL, arguably most of the benefits (and suffering) derived from having a child are not health-related, but has more to do with wellbeing, living a meaningful life and achieving life goals (68–70). However, infertility treatment is a medical intervention that competes for healthcare funding within a HTA framework and is thus further disadvantaged in terms of the utility/disutility captured by QALYs. The need to capture broader benefits of healthcare intervention, such as wellbeing, is increasingly being recognized (79) and has led to initiatives such as the *Extending the QALY* project which aims to develop a broader QALY measure (EQ-Health and Wellbeing, EQ-HWB) (80).

## Cost-benefit framework as alternative to assess value for money

In the absence of broader validated preference-based measures (e.g., EQ-HWB) that are applicable to unborn life, CBA is a more appropriate method for assessing the value for money of infertility treatments (68–70). In a CBA both costs and benefits of an intervention are monetized and, therefore, can be compared directly and the net monetary benefit (NMB) derived (NMB = benefits–costs). Interventions for which the NMB is positive represent good value for money as benefits outweigh costs. To monetize the benefits of an intervention, WTP values for a child created through infertility treatment are elicited (based on stated preferences in hypothetical questions) or observed (based on market behavior). However, while the latter is often preferred, the derivation of WTP values for infertility treatment based on observed market behavior is limited because price signals in healthcare markets are often highly distorted by insurance and confounded by the ability to pay (81). Alternatively, WTP values can be derived using hypothetical stated-preference methods, the most common being discrete choice experiments (DCEs). In these survey-based experiments, respondents choose their preferred treatment scenario in a sequence of choice tasks, where each treatment is described in terms of its key characteristics. In the case of infertility treatment, these characteristics would include success rates (i.e., chance of a live birth) and cost (i.e., cost of one ART cycle). Thereby respondents implicitly reveal their trade-off between the success rate and costs. Respondent choices capture a much wider utility function than HRQoL, including the intrinsic value of a newly created life and, if required equity and ethical preferences, thus overcoming a number of limitations of QALYs. The marginal rate of substitution then allows the value for a statistical baby (VSB) to be derived (82), much in the same way that a value of a statistical life (VSL) is derived. The VSL is an established economic concept used to inform policy in a variety of areas including public resource allocation to transport and environmental investment (83).

A DCE conducted among taxpayers in Australia illustrates this approach: Botha (84) reported that an average taxpayer was willing to pay $2.23 per year for a 1% improvement in the chance of having a baby per infertility treatment cycle. Applying a similar concept as the VSL, the VSB can be derived as the WTP value divided by the change in the treatment success rate (i.e., $2.23/1%) resulting in a WTP per statistical baby of $223 per taxpayer. This VSB could then be used in a CBA to monetize infertility treatment success (i.e., the birth of a baby). Comparing this value to the cost of infertility treatment for the creation of one baby establishes whether treatment represents value for money. By extension, the value for money of different eligibility criteria for public funding (e.g., age and number of ART treatment cycles) can be evaluated to inform resource allocation. That is, the number of ART cycles funded would be limited to those where the cost of treatment does not exceed the taxpayers' WTP for a statistical baby.

While introducing a CBA framework in HTA assessments moves closer to capturing the true value of reproductive interventions, such as infertility treatment, and explicitly allows the NMB to be derived, decision rules would still be needed to decide how many QALYs from other health interventions should be forgone to fund such interventions. However, given the increasing recognition that many healthcare interventions have significant non-health benefits, this is perhaps inevitable (85).

Indeed, the increasing reliance on HTA for decision-making in health systems globally and the increasing recognition of the limitations of QALYs and current WTP thresholds requires alternative approaches to assess value-for-money by HTA organizations. There are currently no specific best-practice guidelines for cases where QALYs or current tools such as the EQ-5D are not fit-for-purpose. For instance, a recent NICE methods review found that there "is currently no guidance on what to do if EQ-5D is not available in the clinical trials or the literature, and it is not possible to map from another measure to EQ-5D" (86). In general, the NICE guidelines manual advises the use of a CUA framework where QALYs are applicable or, otherwise, a cost-effectiveness framework using cases averted or a disease-specific outcome as effectiveness measure (87). A criticism of CBA is that they do not consider equity and distributional concerns (88, 89), however this is also true for CUA in its standard form, and, if DCEs are used to derive the WTP thresholds, equity considerations can be implicitly incorporated. Rather, a key reason why HTA agencies reject CBAs seems to be the lack of guidelines on how results of a CEA, CUA and CBA can be compared to make resource allocation decisions (90).

There are a growing number of exceptions and exclusions to using the standard HTA framework. A case in point is the emergence of high-cost disease modifying therapies for rare diseases where WTP thresholds of up to $500,000 are considered acceptable (73, 88). Other concerns about the standardized use of QALYs include that they disadvantage those who are severely ill, disabled and are at the end-of-life, as well as not incorporating equity and distributional concerns in their standard form. A number of authors have proposed modifications to the current QALY-based HTA framework or proposed a wider use of cost-consequence studies (89–92). Such limitations have also prompted reviews of current HTA frameworks including in Australia (93) and the UK (94, 95).

## Conclusion

Infertility treatment competes with other medical interventions for healthcare funds within a HTA framework but is uniquely assessed based on its ability to create life, rather than improve, extend, or save existing life. CUAs measuring treatment outcomes in QALYs are not fit-for-purpose to evaluate infertility treatments. Therefore, appropriate methods that holistically capture health *and* non-health benefits to assess the cost-effectiveness of infertility treatments are required. McIntosh (96) described how WTP values for treatment outcomes derived from a DCE can be used in a CBA over 15 years ago. However, even though the number of DCEs have increased significantly over this time, their results are rarely applied in a policy-relevant context. It is increasingly being recognized that broader benefits beyond health should be considered when assessing value for money in healthcare. Therefore, it is important that the health economic research agenda develops standards and best-practice guidelines for the incorporation of DCEs and CBA into HTA (97), including how CBA results should be compared to those obtained using CUAs to allocate healthcare funding.

## Author contributions

EK and GC contributed to the conception and design of the article. The first draft of the manuscript was written by EK, and all authors commented on the previous versions of the manuscript. All authors contributed to the article and approved the submitted version.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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