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human reproduction **OPINION**

Modelling futility in the setting of fertility treatment

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ABSTRACT: When is a fertility treatment futile? This question has great practical importance, given the role futility plays in ethical, legal and clinical discussions. Here, we outline a novel method of determining futility for IVF treatments. Our approach is distinctive for considering the economic value attached to the intended aim of IVF treatments, i.e. the birth of a child, rather than just the effects on prospective parents and the health system in general. We draw on the commonly used metric, quality-adjusted life years (QALYs), to attach a monetary value to new lives created through IVF. We then define futility as treatments in which the chance of achieving a live birth is so low that IVF is no longer a cost-effective intervention given the economic value of new births. This model indicates that IVF treatments in which the chance of a live birth are <0.3% are futile. This suggests IVF becomes futile when women are aged between 47 and 49 years of age. This is notable older than ages currently considered as futile in an Australian context (∼45). In the UK, government subsidized treatment with the couple's own gametes stops at the age of 42, while privately funded treatments are self-regulated by individual providers. In most European countries and the USA, the 'age of futility' is likewise managed by clinical consensus.

Key words: futility / assisted reproduction / bioethics / mathematical modelling / cost-effectiveness / quality-adjusted life years

Introduction

'Doctor, for my whole life, I have dreamt about being a mother and having my own child. I understand that my chances are low at my age, but my desire to be a mother is overwhelming. Even if you were to tell me that my chance of having a baby was one in a million, I would still like to try. I simply must do everything I possibly can to try to make this dream come true'. (Hypothetical Patient A)

The quote above is from a hypothetical patient affected by infertility and is a common sentiment expressed by patients who may be approaching the end of their reproductive life. It is often said that a mother's love knows no bounds, and so too is some people's desire to have children. Modern technology has come a long way since the birth of the first 'test-tube' baby, Louise Brown, in 1978 (Steptoe and Edwards, 1978). However, many women are delaying attempts at becoming pregnant. The result is that many patients seek IVF when their chances of conception are very low (Faddy *et al.*, 1992; Mehlmann, 2005). For example, at age of 40, there is a 10% chance of having a live birth (Schwartz and Mayaux, 1982). At some point, fertility treatment would offer such a low chance of success that it is not offered. This is sometimes justified on the grounds that such treatments are 'futile'. This is devastating to couples who strongly desire to have a child.

Futility

In Australia, most IVF cycles are performed in the private sector with financial subsidy from the government via the Medicare and PBS Systems. According to the latest available estimates, fertility treatments were subsidized by AU$245 million in 2016 (Tremellen and Savulescu, 2017). In order to obtain these subsidies, patients need to be diagnosed as being 'medically infertile' and treatment needs to be 'medically necessary', by their fertility specialists (Department of Health and Commonwealth of Australia, 2020). While it is agreed amongst the profession that it would be unethical to offer treatment that is futile, the definition of futility is not universally accepted. For example, the largest providers of fertility services in the Australian State of Victoria, Melbourne IVF and Monash IVF, would not offer treatment with autologous gametes (obtained from their bodies, as opposed to gametes obtained from a donor) to women over the ages of 46 and 45 years old, respectively (Victorian Assisted Reproductive Treatment Authority (VARTA), 2020). These limitations derive from a consensus decision of clinicians within these companies based on a combination of previous experience, perceived chance of success and the belief that the risks of treatment above these ages outweigh possible benefits, and is therefore not in the patients' best interests. Even if patients are willing to accept the full cost of treatment, forgoing government subsidies, it is simply not offered, based on the consensus opinion that the chance of success is so low that the treatment is deemed to be futile. This is reflective of the nationwide practices in Australia (Chambers et al., 2017). In the UK, the National Institute for Health and Care Excellence (NICE) (2017) recommends that IVF treatments should be offered by the NHS at no additional cost to the patient according to the following scenarios:

> *In women aged under 40 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 3 full cycles of IVF, with or without ICSI. If the woman reaches the age of 40 during treatment, complete the current full cycle but do not offer further full cycles.*
>
> *In women aged 40–42 years who have not conceived after 2 years of regular unprotected intercourse or 12 cycles of artificial insemination (where 6 or more are by intrauterine insemination), offer 1 full cycle of IVF, with or without ICSI).*

The cost-utility analysis includes the benefits that a child might bring to the mother and no other considerations. The ESHRE, which is considered a peak body representing the fertility treatment sector in Europe, has no recommendations as to what constitutes futility and under what circumstances treatment can or should be refused due to its perceived inability to achieve the desired outcome.

In the USA, the American Society of Reproductive Medicine (ASRM) issued guidelines in 2019 to address what it would consider a 'futile treatment' that can justifiably be refused. These guidelines define futility as 'situations in which a given treatment has virtually no chance of achieving the desired medical end' (ASRM, 2019).

Furthermore, the ASRM clarifies these guidelines in the fertility context:

> *Where the desired physiologic goal is a live birth and there is no or virtually no reasonable likelihood that this goal will be achieved through the proposed treatment.*

The guidelines define futility as the chance of a live birth being less or equal to 1%. Unfortunately, there is no justification for why a figure of 1% is chosen, and the guidelines themselves state that 'there are no clear indices of futility in the fertility context' (ASRM, 2019). The idea of a 1% chance of success as the cut-off for futility appears to originate from a paper in 1990 on end-of-life care, wherein the rationale given for the cut-off of 1% is 'if a treatment can be shown not to have worked in the last 100 cases, we propose that it be regarded as medically futile' (Schneiderman et al., 1990). However, the relevance of a 1% cut-off in a fertility context is unclear.

In the years that followed, several papers used a 1% 'futility rule' (Schneiderman and Jecker, 1993; Jecker and Schneiderman, 1995; Schneiderman et al., 1996). The 1% rule has been criticized as paternalistic, attempting to increase the power of medical professionals over patients, thereby depriving them of autonomy (Truog et al., 1992; Brody and Halevy, 1995). Furthermore, previous research indicates that 'futility' has a variety of meanings to different individuals, even those working in the same department (White et al., 2016). Hence, there is a need to move to draw on more detailed and justified definition of futility in the fertility contexts to enable a more standardized approach to offer fertility treatments. In this article, we outline a novel method of approaching futility calculations in fertility treatments.

Futility, quality-adjusted life years and the value of life

One way of approaching the subject of futility, is to ask: when is the chance of success not worth the investment? This has two dimensions: the interests of the patient and the interests of society (or the healthcare provider). Savulescu has argued that futility is best understood as a concept of when distributive justice precludes treatment (Wilkinson and Savulescu, 2011, 2018). This can be applied across different treatments, to enable consistent judgements to be made by setting a cost-effectiveness threshold; in this way, futility can be consistently applied to intensive care or cardiac surgery (see Wilkinson and Savulescu, 2014; Wilkinson and Nair, 2016; Wilkinson et al., 2018). To apply this to fertility treatments, we need a way of measuring the value of the new lives that potentially result from IVF that is independent of their instrumental effects on the parents.

In other areas of medicine, the value of years of life is measured through the metric quality-adjusted life years (QALYs). This measure takes 1 year of life, in good health, to be worth 1; and a year of life in a suboptimal state to be worth some value <1, depending on how badly quality of life is affected. QALYs are extensively used in an Australian setting by the Pharmaceutical Benefits Advisory Committee (Department of Health and Commonwealth of Australia, 2016) and the Medical Services Advisory Committee (Department of Health and Commonwealth of Australia, 2017) in their deliberations regarding which medications and treatments should be subsidized. Furthermore, on the international level, the World Health Organisation (WHO) strongly advocates use of QALYs for healthcare-related decision-making on a national level (WHO Commission on Macroeconomics and Health & World Health Organization, 2001).

It has been postulated in the past that cost-utility analysis, based on the concept of QALYs, is unsuitable for assessing fertility treatments because it is designed to measure health and life-expectancy changes affecting living patients. In effect, the QALYs generated by a child cannot be considered because one cannot improve or in any way affect the well-being of someone who is yet to be conceived (Devlin and Parkin, 2003; Chambers et al., 2013). As put by Nancy Devlin (Devlin and Parkin, 2003):

> *QALYs are intended to capture improvements in health among patients. They are not appropriate for placing a value on additional lives. Additional lives are not improvements in health; preventing someone's death is not the same as creating their life and it is not possible to improve the quality of life of someone who has not been conceived by conceiving them.*

Devlin here begs the question. There is a large philosophical literature that supports reasons to create new lives (including various forms of utilitarianism) as well as a vast literature that argues there is no reason to create new life. For example, in his work 'Death and the Afterlife', Scheffler (2013) argues that the capacity of individuals living today to live good and meaningful lives depends on the continued existence of humankind into the future. Thus, the interests of people today depend on the fact that new people are born and thus that new lives are created. Conversely, in his work 'Better Never to Have Been', Benatar (2006) argues it is wrong to bring new people into existence, drawing on an ethical view where the avoidance of harm is of greater importance than providing benefit. This is one of the unresolved issues of population ethics.

Indeed, it may be difficult to compare the value of prolonging an existing life with creating a new life and QALYs may be an inappropriate measure to facilitate that. However, within fertility treatment, QALYs may be useful for comparing different interventions or treatment of different groups.

Thus, just because the concept of QALYs was devised as a metric to be used in the context of treatment of disease, does not mean it cannot be repurposed for futility calculations in fertility treatments when comparing fertility treatments. Compare two IVF treatments: treatment A causes a child to be born with a life expectancy of 80 years, while treatment B causes a child to be born with a life expectancy of 40 years. It's intuitively plausible to say that B is half as good or effective as A as a medical intervention. This is completely separate from the impact of A and B on maternal distress or preferences, or from the comparison of these with lifesaving treatments. B is a poor treatment compared to A because it is, in some sense, less effective at creating new life. The use of QALYs helps capture this intuition. A cost-utility analysis utilizing QALYs attributed to a child born can thus be drawn on to assess cost-effectiveness of IVF and compare it to other health interventions.

A new approach to determining when IVF in futile

Drawing on the considerations of cost-effectiveness described above, we would like to describe a novel approach to calculating futility for the purpose of IVF. Our method relies on three different thresholds.

Value Threshold (VT)—the total monetary input a society is willing to expend to achieve one live birth through fertility treatment (e.g. IVF), above which treatment is considered futile.

Effectiveness Threshold (ET)—the chance of a treatment producing one live birth, below which a treatment would be considered futile.

Age Threshold (AT)—age of a woman above which the chance of live birth is below the ET, and therefore treatment above that age is futile and should not be offered.

These thresholds are interrelated and will be addressed in turn.

Value threshold

Fertility treatments are unique in that they aim at the creation of a new life. Above, we argued that one way to measure the value of this outcome was to combine life expectancy and expected quality of life at birth. Life expectancy at birth in Australia is currently 82 years (Australian Institute of Health and Welfare and Commonwealth of Australia, 2021). Commonly, not all these years will be spent in perfect health. A comprehensive report on the quality of life at various ages and overall was published in 1999 (Kind *et al.*, 1999). There are also extensive data available on population preferences related to quality-of-life measurements which allow for calculation of a QALYs index at birth (Hanmer *et al.*, 2006; Revicki, 2006). Based on these reports, it can be estimated that in order to convert life expectancy at birth to the total number of QALYs, it is necessary to adjust the years value by 0.86 for the population overall. It can be argued that IVF-conceived babies may in fact have a lower QALY number due to slightly increased risk of disability, mostly related to the increased risk of twin pregnancies, compared to the general population (Ludwig *et al.*, 2006). A small adjustment can be made to account for this irregularity by a QALY adjustment of 0.06, compared to the value of 0.86 reported for general population. The total number of QALYs that are associated with an IVF birth, in Australia, is therefore:

$$82 \times 0.8 = 65 \text{ QALYs}.$$

In order to arrive at the VT, the next step is to determine a monetary value that corresponds to these 65 QALYs.

Multiple sources provide surprisingly uniform estimates on the value per QALY a society is willing to pay, but it does vary, depending on the country in question. In Australia, the value appears to be in the range of AU$50 000 per QALY gained. This is based on the fact that novel pharmacological treatments are more likely to be subsidized if they produce benefits below that threshold (George *et al.*, 2001). There is a long history of how the value of a QALY is measured. It appears that it first gained prominence in the USA in the 1970s, when treatment of end-stage renal failure with dialysis was mandated for Medicare recipients. The cost-effectiveness ratio for this intervention at the time was approximately US$50 000 (Neumann *et al.*, 2014). There are continuous efforts by economists and researchers to refine this estimate and to provide a more accurate assessment of society's willingness to pay for health interventions, based on economic theory as well as empirical evidence (Hirth *et al.*, 2000; Braithwaite *et al.*, 2008; Weinstein, 2008). The most comprehensive study available to date, which investigates the cost-effectiveness threshold that a society is willing to pay for a QALY gained, was performed by Takeru Shiroiwa and colleagues in 2010 (Shiroiwa *et al.*, 2010). Based on an extensive survey administered internationally, the researchers were able to arrive at the threshold value of how much different societies are willing to pay for one QALY gained as a result of a medical intervention. For Australia, the value was AU$64 000 and for the USA, it was US$62 000. There are variations that must be taken into account, such as exchange rates and the effect of inflation. Nevertheless, a threshold value of AU$50 000 per QALY gained seems to be reasonable and on the conservative side. It is therefore practical to assume that this value can be used to estimate the total monetary value that Australian society is willing to pay for a child produced with the help of medical intervention such as IVF.

An alternative method of estimating the value of one QALY to the health system is proposed by the WHO. As the overall wealth of a nation is variable, a value of QALY in an advanced economy should be higher than the equivalent gain in QALY in a less developed economy. To account for economic disparity in available healthcare resources, the WHO proposed to value one QALY gained at one to three times gross domestic product (GDP) per capita per year (WHO Commission on Macroeconomics, Health & World Health Organization, 2001). These values are in the public domain and can easily be obtained. For example, GDP per capita per year for Australia is $50 000 which fits nicely with the value discussed above (Central Intelligence Agency (CIA), 2021). It is important to consider the effect with the least economically developed countries, for example Liberia, where the comparative value is only US$1400 (Central Intelligence Agency (CIA), 2021). Furthermore, life expectancy in Liberia is 63 years at birth, fewer than the life expectancy in Australia. The risk of life with disease or disability is probably also higher and therefore, a similar discount would apply, resulting in a newborn baby contributing only 40 QALYs to the healthcare system. This is helpful, as it illustrates the vastly diverse outcomes of this model, depending on the inputs.

Now that the threshold value of QALYs gained is established (herein assigned the symbol T), it is possible to use the number of QALYs (N) to derive a VT for of a child born with the help of IVF. The VT is simply:

$$VT = N * T.$$

In an Australian setting, this is simply:

$$VT\ (\text{Australia}) = 65 * AU\$50\ 000$$

VT (Australia) = AU$3 250 000

This represents the threshold cost, above which, the achievement of a live birth would no longer be cost-effective. It is important to note, however, that this value should only be used in defining futility and in no way does it imply or advocate that the average cost of an IVF-conceived child should approach this limit.

In the next section, an attempt will be made to arrive at the 'Effectiveness Threshold', below which treatment can be refused as it would be considered futile.

Effectiveness threshold

This threshold will produce an estimate of how effective a cycle of IVF should be (in terms of achieving a live birth per cycle) in order to be considered as cost-effective, which will in turn be used to define futility. In doing so, it will be necessary to estimate the cost of a cycle of IVF. It is difficult to measure the total cost of an IVF treatment, including direct and indirect costs. Numerous researchers have attempted to do this with varying degrees of success. The main problems are variation in direct costs between clinics, public and private components of the direct costs, as well as multiple ill-defined indirect costs, such as loss of productivity while treatment is undertaken (Dixon et al., 2008). A very rough estimate prices the cost of a cycle at AU$10 000 in the Australian setting, which includes private contributions as well as public subsidies. It covers the direct costs of treatment, but the estimate is high enough to include indirect costs, as they appear to be small. This estimate will vary significantly from clinic to clinic and even more so from country to country. For example, it appears that in health systems with third-party payers, the cost is less (e.g. in Israel, at about US$6000) compared to mostly privately funded health systems (e.g. the USA where the cost per cycle is estimated at US$14 000; Collins, 2002). For the cost estimation to be even remotely accurate, local conditions need to be taken into account, but an overall cost of $10 000 per IVF cycle in Australia seems reasonable (Connolly et al., 2010).

With the assumed cost per cycle of AU$10 000 (henceforth referred to as C, for Cost), it is now possible to calculate the ET, which is derived from the VT divided by the Cost per IVF cycle (C), converted to a percentage:

$$ET = \frac{1}{\frac{VT(in\ AU\$)}{C(in\ AU\$)}} * 100\%.$$

In the Australian setting, with the assumed cost per cycle being AU$10 000:

$$ET = \frac{1}{325} * 100\%$$

$$ET = 0.3\%.$$

Therefore, it can be stated that if a cycle of IVF in Australia has <0.3% chance of producing a live birth, it is no longer cost-effective, and thus futile on our proposed model.

One limitation of the ET is that it is extremely difficult to estimate the chance of success for an individual patient. However, there is one group of patients for whom these threshold values would be useful. In the upper extreme of reproductive life, it is in fact possible to accurately estimate the likelihood of an IVF cycle producing a live birth (Esteves et al., 2021; Richters et al., 2022; Bercovich et al., 2022). Once the chance of producing a live birth per cycle at different ages is calculated, it will be possible to arrive at the final AT. This will be done by applying the ET to the age-dependent chance of live birth per cycle of IVF. This will allow for an estimation of age at which treatment becomes futile, where the chance of success falls below the previously calculated ET.

The next question to be addressed is how to determine at what age the pregnancy rate falls below this threshold of 0.3% per cycle making treatment futile, as it is no longer cost-effective based on agreed standards of cost-effectiveness being $50 000 per one QALY gained.

Estimation of IVF effectiveness at the upper extreme of reproductive age

There are a number of sources of data related to effectiveness of IVF in Australia. These include state-based registries (such as the Victorian Assisted Reproductive Treatment Authority (VARTA), 2020 in Victoria) as well as national databases (such as the Australian & New Zealand Assisted Reproduction Database (ANZARD) maintained by the University of New South Wales (National Perinatal Epidemiology and Statistics Unit, 2019)). One of the problems is that there are very few IVF cycles being performed at the upper extreme of reproductive life, i.e. in women over 45 years of age. Therefore, it is difficult to reliably estimate the success rates in women above this age. An alternative and perhaps more reliable estimate can be obtained by examining a large database of IVF treatments and outcomes maintained by a single large fertility centre. To investigate this further, the database of Melbourne IVF was examined (approval was obtained for this exercise

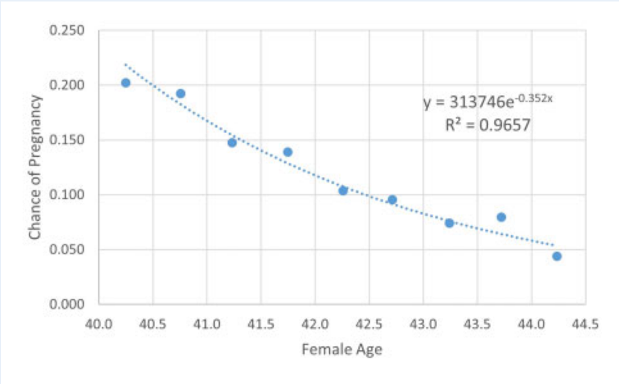

Figure 1. Chance of clinical pregnancy per IVF cycle for women between 40 and 44.5 years old.

from the Melbourne IVF Ethics Committee). All data used were de-identified and are available in the Public Domain in the form of Annual VARTA reports (Victorian Assisted Reproductive Treatment Authority (VARTA), 2020)). This database contains all treatments undertaken by Melbourne IVF over the past 10 years and contains outcome data for women up to the age of 46. The entire database was examined, and cycle and outcome data were extracted for women between the ages of 40 and 45. All subjects had outcomes of IVF cycles recorded as either having no viable pregnancy or foetal heart seen at the first ultrasound after treatment at 6+ weeks of gestation. These data were graphed, and a best-fit curve was produced, which allowed for an equation to be calculated, using the presence of a foetal heart as an outcome variable (see Fig. 1).

The equation that describes this best-fit curve is:

$$\text{Foetal heart per embryo transferred (effectiveness threshold)} = 31\,3746e^{-0352\times AGE}$$

This gives an extremely accurate estimate as the best-fit curve, on which this equation is based, has an $R^2 = 0.95$ indicating an almost perfect fit. It can be stated that due to the nature of the population in question and considering the biological processes taking place, the rate of exponential decline in the live birth rate will continue beyond the age for which reliable data are available. In other words, the graph and the corresponding equation can reliably be used to estimate either success rate or age, provided one of these values is known, beyond values for which actual data are available.

In order to allow for calculation of age at which treatment becomes futile or not cost-effective, the above equation can be expressed as:

$$\text{Age Threshold(AT)} = \frac{\ln\ (\text{Foetal heart per embryo transferred (ET)} \div 313\,746)}{-0.352}$$

OR

$$(\text{AT}) = \frac{\ln(\text{ET} \div 313\,746)}{-\ 0.352}.$$

There are two further adjustments that are required to arrive at the accurate estimate of age at which IVF treatment ceases to be cost-effective and therefore, futile, in an Australian context. Firstly, foetal heart per embryo transfer rate is not the same as live birth rate. At the upper extreme of reproductive age, the majority of early pregnancies will result in a miscarriage. It is estimated that at the age of 45, the chance of early miscarriage is about 70% (Magnus *et al.*, 2019). Since this value includes all pregnancies, not confined to ultrasound-confirmed pregnancies with a foetal heart present, this value will be somewhat less for our population. For our modelling, we will initially stipulate this figure to be 50%, so that the chance of a live birth following pregnancy where a foetal heart rate is seen at 6 weeks of gestation is 1 in 2.

Secondly, it is also well known that not all IVF cycles started will result in an embryo transfer. The discount rate to account for these cycles without ET appears to be in the order of 50% as well (Shrem *et al.*, 2022). Therefore, to account for all these discounts and to arrive at the most accurate estimate of the age at which treatment should not be undertaken, foetal heart rate per embryo transferred should be multiplied by three to arrive at the live birth rate which can be used as is shown below to derive an age cut-off for treatment:

$$\text{AT} = \frac{\ln(\text{ET} \times 3 \div 313\,746)}{-\ 0.352}$$

with the stipulation that only 50% of cycles started will result in ET and only 50% of pregnancies which have a detectable foetal heart at 6 weeks will continue to a live birth. In order to achieve a live birth rate of 0.3%, there needs to be 0.9% chance of a foetal heart rate per cycle started. This can be expressed as:

$$\text{AT} = \frac{\ln(0.003 \times 3 \div 313\,746)}{-\ 0.352}$$

AGE threshold = 49 years

The two stipulations in our model, which attempt to address early pregnancy loss and IVF cycles that do not result in embryo transfer, are obviously questionable. It is beyond the scope of this article to estimate these values precisely. Interestingly, even if the rate of early pregnancy loss is assumed to be 75% and the proportion of stimulated cycles without ET is also increased to 75%, the equation above will look like this:

$$\text{AT} = \frac{\ln(0.003 \times 7 \div 313\,746)}{-\ 0.352}$$

AGE threshold = 47 years

In this scenario, the assumptions are that only 25% of cycles started will result in an ET, and only 25% of pregnancies that have a detectable foetal heart at 6 weeks will continue to live birth. Thus, in order to achieve a live birth rate of 0.3%, there needs to be 2.1% foetal heart rate per cycle started.

Summary and conclusion

In this article, we have defined futility of IVF treatment in terms of cost-effectiveness, determined via reference to the economic value assigned to a live birth. This was done by utilizing QALYs and cost-utility analysis. Using QALYs, it is possible to derive a number of thresholds that can in turn be used to define futility.

To summarize our model, as it applies to the Australian setting, we made the following assumptions:

Life expectancy at birth in Australia: 82 years.
QALY adjustment factor at birth: 0.8.
Acceptable cost per QALY gained: AU$50 000.
Cost of an IVF cycle: AU$10 000.

It follows that an IVF treatment is futile when it has a lower than 0.3% chance of being successful. When these inputs are used, the cut-off age at which IVF treatment becomes futile is between 47 and 49 years, depending on the assumptions used for cycles started without resultant embryo transfer and the probability of miscarriage, once foetal heart is detected at the initial ultrasound. This is higher than standard Australian practice of ceasing treatment with autologous oocytes between the ages of 45 and 46 years.

Whilst it is clear that the assumptions used in these calculations are open to criticism, the model is both plausible and novel. More accurate estimates of inputs could improve the accuracy of the model, as well as test it in other settings. The model presented is intended to illustrate the possibility of using QALYs and some aspects of cost-utility analysis to derive objective definitions of futility that are based on accepted societal values and are derived in a transparent and replicable manner. To our knowledge, this is the first method of defining futility in the IVF setting, taking into account the intrinsic economic value of a child produced with the help of IVF. The VT and ETs are of purely theoretical usefulness and are not designed to be utilized in day-to-day fertility practice. The AT, on the other hand, can be used to establish an objectively derived age cut-off, above which treatment would be considered futile and therefore, not offered.

Authors' roles

All authors substantially contributed to the concept, writing and revision, and final preparation of this manuscript.

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Conflict of interest

A.P. is a fertility specialist and holds a non-controlling Interest (equity) in Virtus Health. J.S. is supported by the Wellcome Trust (WT203132). He is a Bioethics Committee Member for Bayer Pharmaceutical Company and a partner on a grant co-funded by Illumina, but no funds are received by him or his Institution from this grant. There are no other conflicts of interest to declare.

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