Reducing the incidence of twins from IVF treatments: predictive modelling from a retrospective cohort

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BACKGROUND: IVF treatments carry a high risk of twin pregnancy which confers a higher risk to the mother and child than singletons. Increased use of elective single embryo transfer (eSET) can reduce this twin rate. We aimed to utilize a previously published data set and statistical model based on routinely collected clinical data to predict the outcomes of policies that increase the proportion of eSET.

METHODS: The models allow simultaneous prediction of outcomes from double embryo transfer (DET) and SET. These models were used to predict outcomes for different scenarios using SET in both the initial (fresh) transfer and over a complete cycle (transfer of all embryos created, with cryopreservation). A total of 16,096 cycles (12,487 fresh and 3,609 frozen) from 9,040 couples treated between 2000 and 2005 were included in the final analyses.

RESULTS: For any transfer, SET has about a one-third lower live birth rate relative to DET: this can be partially mitigated by appropriate patient and treatment cycle selection, with several realistic policies performing similarly. However, if we consider complete cycles with embryo cryopreservation, it is possible for repeat SET to produce more live births per egg retrieval than repeat DET.

CONCLUSIONS: All patients receiving SET would have a higher chance of successful treatment in that cycle if they received DET. The selection of appropriate patients for SET can partially ameliorate the overall loss. For complete cycles, repeat SET could produce more live births per egg retrieval than repeat DET. All treatments involving SET will increase the number of treatments required to achieve a successful outcome and this extra treatment burden will be a significant barrier to the implementation of such treatments.

Key words: IVF / embryo transfer / twins / predictive models / cohort study

Introduction

While the fecundity rate for infertile couples undergoing IVF treatment is higher than the conception rate in a normal population, the overall live birth rate (LBR) is still relatively low at 29% per fresh treatment cycle (Andersen et al., 2009). Where treatment is successful, there is a high rate of twins, which in turn carry a higher risk of adverse maternal and infant morbidity and mortality. This high twin rate occurs because of the common practice of transferring multiple embryos (in most European countries, this is limited to two in all but exceptional circumstances) in each treatment cycle to improve success rates. In many countries, this has led policy-makers to limit the number of embryos transferred to one (single embryo transfer, SET) for at least specified patient groups (Ombelet et al., 2005; Saldeen and Sundstrom, 2005; De Neubourg et al., 2006; Cutting et al., 2008; Andersen et al., 2009). Introduction of a SET policy following IVF has been shown to lead to a dramatic improvement in neonatal and maternal outcomes (Kallen et al., 2010b). The need to...
reduce the number of twins is accepted by many clinicians and professional bodies (Cutting et al., 2008), but not universally (Gleicher and Barad, 2009). In addition, many patients remain sceptical, viewing twins as an ideal treatment outcome (Gleicher et al., 1995; Goldfarb et al., 1996; Pinborg et al., 2003; Porter and Bhattacharya, 2005).

Current practice and guidelines where SET is advocated (Cutting et al., 2008) are based on the premise that acceptable treatment success rates can be achieved and twin rates reduced if SET is used in appropriately selected patients and more use made of embryo cryopreservation. However, there is only very weak evidence to support any particular policy, and the few successful clinical trials that have been conducted are not very informative (Pandian et al., 2005). IVF treatments are very closely monitored by clinics and regulatory authorities, which collect a large amount of data on patients and treatments, and so a rich source of information is available to address questions about the best use of SET to reduce twin outcomes.

In a previous paper (Roberts et al., 2010a), we described the development of a statistical model, utilizing the ‘embryo-uterus’ (EU) framework based on detailed data from a number of UK IVF units over the 2000—2005 time period. Allied to this modelling work were qualitative studies of patient perspectives that both informed the modelling process and reviewed the modelled outcomes. The overall aim was to utilize these models and the insights from the work with patients to investigate policy options around the selection of patients for SET and the use of embryo cryopreservation in terms of both the clinical outcomes and patient acceptability. Here, we investigate strategies for selecting patients for SET or double embryo transfer (DET) in the initial fresh transfer, and strategies that consider the complete treatment cycle, i.e. the replacement of all embryos created following an egg-retrieval procedure over the fresh and a series of frozen embryo replacement cycles.

### Materials and Methods

A summary of the methodology is given below. Further details are available elsewhere (Roberts et al., 2010b).

### Statistical models

As described previously (Roberts et al., 2010a), predictive statistical models were developed for treatment outcomes based on routinely collected data from five UK treatment centres covering the range of UK practice and including National Health Service, fee-paying and private centres. A total of 16,096 cycles (12,487 fresh and 3,609 frozen) from 9,040 couples treated between 2000 and 2005 were included in the final analyses.

### Predictions

The EU modelling framework explicitly considers the fate of each individual embryo; so it is possible to estimate outcomes for different numbers of embryos transferred, with the assumption that the embryos are independent after inclusion of uterine effects and embryo covariates (note that this means that correlations between embryos in the same cycle are explicitly included through the uterine effects and by sharing common covariates). For those patients who received DET, we compute the outcomes if only the most viable embryo were transferred. These estimates are then used to predict the outcomes of a range of different patient-selection scenarios, identified from discussions with clinicians, in-depth interviews with patients and the literature. In-depth interviews with patients provided the context to this study, informing the selection of treatment scenarios, and end-points and are described in detail elsewhere (Roberts et al., 2010b). In order to compute the outcomes under each scenario, the sets of patients to receive SET or DET under that scenario were identified from the full patient data set and the success and twin rates computed accordingly from the model.

The models relate to individual embryo-transfer procedures. In order to estimate the outcomes of treatments that involve multiple embryo-transfer procedures, we employed a simulation model that utilized the single transfer predictions, the estimated inter-cycle correlations, the estimated losses resulting from cryopreservation (the proportion failing to survive the freeze/thaw process and the lower viability of those that do survive) (Cutting et al., 2009) and the distribution of embryo quality for all created embryos from another study (Brison et al., 2004). Briefly, the outcome of each patient in the sample was computed on the basis that all embryos created were transferred over a number of DET or SET transfers. The first transfer was a fresh embryo and the success probability was computed as above. Subsequent frozen cycles used the model above but attenuated as defined below. The embryo grades were sampled from the distribution of unselected embryos from a previous study using the same grading scheme (Brison et al., 2004). Initially, the best one or two embryos were transferred, and the remainder retained, subject to a minimum quality (grade) constraint. Embryos were then considered to be thawed in batches, with a given proportion assumed to fail the thawing process (simulated from a binomial distribution) and the best-quality embryo(s) transferred and the others discarded. The simulations presented here assume small batches are thawed containing either the number to be transferred or that number plus a spare. If only one embryo were available for a DET cycle, a SET cycle was simulated. A patient-level random effect consistent with the modelled data was included to allow for correlations between cycles in the same couple, this being sampled from a normal distribution.

A range of losses caused by freezing/thawing were considered, parameterized by the loss in embryo viability (attenuation) and the probability that an embryo survives the freeze/thaw process. The loss in viability was varied over the range seen between the centres in the data set along with no loss, and the probability of freezing failure ranged from 10 to 25% (Cutting et al., 2009). Three sets of parameters are shown, approximately corresponding to the range of values seen in our data: ‘Poor’ with high loss in viability and 25% freezing loss; ‘good’ with low loss in viability and 10% failing to thaw; and ‘perfect’ freezing with no losses. Twenty thousand cycles were simulated to give an expected 95% confidence interval on an estimate of 20% of ± 0.5%.

All computations utilized custom-written code in the R statistical computing environment (R Development Core Team, 2008).

### Results

#### The fresh cycle

Overall, for the initial fresh transfers, the LBR in this data set would have been reduced from 24.3 to 16.5% if all the patients who received DET had received one embryo. Figure 1 shows the ratio of LBR in SET:DET transfers (68%), along with the same ratio computed from the six available randomized trials directly comparing SET with DET. This shows that the modelling process can reproduce the results of the trials, and moreover give more precise estimates of the treatment effects than the relatively small trials.

In Fig. 2, we show the SET: DET LBR as a function of maternal age, showing the range of predicted rates for the actual patients in the data set. Although losses are slightly less for those aged under 30 years,
LBR is reduced by about one-third across all ages if patients receive SET rather than DET in this fresh cycle. Most of the high variability between patients of the same age seen in Fig. 2 is related to the embryo quality, with smaller losses in success where the second embryo is of poor quality.

Selection in the fresh cycle

Outcomes for four representative policies to achieve a 10% twin rate are shown in Table I and compared with randomly selecting patients for SET. The specific policies shown are selection for SET of:

(i) those that the full statistical model indicates are at highest risk of having twins;

(ii) younger patients where they have a good-quality embryo available for transfer;

(iii) younger patients with a top-quality embryo available for transfer and at least four embryos in total available and

(iv) patients with the largest number of embryos available and including at least one good-quality embryo, regardless of patient age.

The latter policy (iv) approximates to selecting for SET based on the number of embryos available for later (frozen) transfer. All the selection policies shown mitigate about half the loss in LBR at a population level incurred in reducing the twin rate from the 25% obtained with DET to 10%. While more complex selection mechanisms, as illustrated using the full statistical model, can achieve a given twin rate with somewhat less SET, the overall LBRs are similar to those with simpler decision rules. It is important to note here that the success rates are those for the population as a whole, each individual patient who receives SET will have a lower chance of success than if they had received DET.

While most clinically suggested policies performed similarly, it is possible to have high rates of SET with high twin rates with inappropriate patient selection. For example, one suggestion arising from discussions with patients was that as younger patients may be more likely to be capable of coping with a twin pregnancy and the subsequent children, that these patients should have DET, and older patients SET: under this scenario, a 10% twin rate would require 79% of transfers to be SET and only achieve a 18.3% LBR.

Complete treatment cycles

A ‘complete’ IVF treatment cycle is defined as the egg retrieval procedure, plus the replacement of all created embryos over a series of fresh and frozen transfer procedures. The results of simulations of

![Figure 1: A comparison of LBR outcomes from IVF trials (estimate with 95% confidence intervals) and predicted outcomes from the EU model developed in unselected patients. The red diamond is the pooled estimate from the trials. The blue diamond and vertical line indicates the predictions from the EU model for patients who underwent DET. (Details of the trials shown here are described in Table III.)](image1)

![Figure 2: Loss in fresh cycle success rate in DET cycles if patients had received SET. Loss is expressed as the ratio of SET/DET LBR and plotted against age (years). The boxplots show the inter-quartile and absolute range of predictions. The thin horizontal line indicates the population average of 68%.)](image2)

**Table I** Numbers of patients required to receive SET in order to achieve a target twin rate of 10% (multiple births per live birth event) for variants of selection using the modelled probabilities.

<table>
<thead>
<tr>
<th>Variant</th>
<th>Threshold</th>
<th>% SET</th>
<th>Live birth rate (%)</th>
<th>Twin rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All DET</td>
<td>0</td>
<td>24.3</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Random selection</td>
<td>–</td>
<td>68.3</td>
<td>19.0</td>
<td>10</td>
</tr>
<tr>
<td>Model-based selection</td>
<td>–</td>
<td>42.5</td>
<td>20.1</td>
<td>10</td>
</tr>
<tr>
<td>Age and embryo quality*</td>
<td>Age &lt;34.3 years</td>
<td>48.2</td>
<td>19.9</td>
<td>10</td>
</tr>
<tr>
<td>Age, embryo quality* and countb</td>
<td>Age &lt;40.5, ≥4 embryos</td>
<td>52.0</td>
<td>19.5</td>
<td>10</td>
</tr>
<tr>
<td>Embryo quality* and countb</td>
<td>≥4 embryos</td>
<td>52.7</td>
<td>19.4</td>
<td>10</td>
</tr>
<tr>
<td>ALL SET</td>
<td>100</td>
<td>16.5</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Random selection is shown for comparison.

*At least one top-quality (Grade 3/4) embryo DET, double embryo transfer.

bNumber of embryos created.

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such complete cycles for a number of exemplar treatment scenarios are shown in Table II. We consider policies of SET or DET throughout (repeat SET/DET), and SET for the fresh cycle and DET for the subsequent frozen transfers, where the number of embryos thawed is the number to be transferred, with or without a spare. Two scenarios for the loss in embryo viability caused by freezing are considered (poor freezing and good freezing, as defined in ‘Methods’ section).

**Table II** Comparison of complete cycle (transfer of all embryos created until a live birth is achieved or there are no more embryos to transfer) SET with DET.

<table>
<thead>
<tr>
<th>Freezing quality</th>
<th>Policy</th>
<th>Final live birth rate (%)</th>
<th>Twin rate (%)</th>
<th>Embryo transfer cycles to achieve live birth (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor freezingb</td>
<td>Repeat SET</td>
<td>27.9</td>
<td>0</td>
<td>2.1</td>
</tr>
<tr>
<td></td>
<td>Repeat SET, thaw spare</td>
<td>25.2</td>
<td>0</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>SET fresh, DET frozen</td>
<td>27.4</td>
<td>2.0</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>SET fresh, DET frozen, thaw spare</td>
<td>26.2</td>
<td>2.8</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Repeat DET</td>
<td>30.9</td>
<td>20.3</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Repeat DET, thaw spare</td>
<td>30.0</td>
<td>21.4</td>
<td>1.3</td>
</tr>
<tr>
<td></td>
<td>Repeat SET</td>
<td>32.3</td>
<td>0</td>
<td>2.4</td>
</tr>
<tr>
<td></td>
<td>Repeat SET, thaw spare</td>
<td>28.5</td>
<td>0</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>SET fresh, DET frozen</td>
<td>31.8</td>
<td>3.8</td>
<td>1.9</td>
</tr>
<tr>
<td></td>
<td>SET fresh, DET frozen, thaw spare</td>
<td>30.0</td>
<td>4.7</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>Repeat DET</td>
<td>33.7</td>
<td>20.2</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Repeat DET, thaw spare</td>
<td>32.3</td>
<td>21.1</td>
<td>1.4</td>
</tr>
<tr>
<td></td>
<td>Repeat DET</td>
<td>41.4</td>
<td>0</td>
<td>2.6</td>
</tr>
<tr>
<td></td>
<td>Repeat DET, thaw spare</td>
<td>35.4</td>
<td>0</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>SET fresh, DET frozen</td>
<td>40.4</td>
<td>9.5</td>
<td>2.0</td>
</tr>
<tr>
<td></td>
<td>SET fresh, DET frozen, thaw spare</td>
<td>37.1</td>
<td>9.9</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>Repeat DET</td>
<td>39.0</td>
<td>20.9</td>
<td>1.6</td>
</tr>
<tr>
<td></td>
<td>Repeat DET, thaw spare</td>
<td>37.1</td>
<td>22.1</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Outcomes if SET is used for all transfers, SET for the fresh and DET for subsequent frozen embryo transfers or DET for all transfers. All patients receive the same treatment, and there is no selection for SET. Options where a spare embryo is thawed to allow for failed thawing are included.

*bTwins per live birth event.

bHigh loss in viability, 25% fail to thaw.

bModerate loss in viability, 10% fail to thaw.

bNo losses related to freezing.

and the (unrealistic) situation, with no freezing losses, is shown for comparison.

If the quality of the cryopreservation is ‘good’, repeat SET can achieve essentially equivalent success rates as DET, while eliminating multiple pregnancies (note that there will be a small number of monozygous twins, which are not accounted for in the modelling process). However, this policy requires approximately one extra transfer cycle. Improving the freezing allows more transfers so the number of transfers increases as freezing improves. The willingness to thaw single embryos, and acceptance of the risk of cancelled cycles, can lead to an improvement in overall LBR over the complete cycle. Alternatively, using DET for the frozen transfers reduces the number of extra cycles significantly and does not generate large numbers of twins. If freezing could be improved, there is scope for repeat SET to significantly outperform repeat DET in terms of LBR as well as virtually eliminating twins. In Fig. 3, we show the repeat SET and DET LBR broken down by patient prognosis, and see that the modelling would predict that if we take a complete cycle perspective, then SET may be appropriate for all patients.

**Table III** Randomized trials comparing fresh SET and DET cycles with embryos transferred on Day 2 or 3.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Number of cycles</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moustafa et al. (2008)</td>
<td>≥ 1 good embryo, Age ≤ 30 years</td>
<td>81</td>
</tr>
<tr>
<td>Van Montfoort et al. (2006)</td>
<td>&gt; 1 embryo, ‘unselected’</td>
<td>308</td>
</tr>
<tr>
<td>Lukassen et al. (2005)</td>
<td>1st treatment, Age &lt; 35 years, &gt; 1 good embryo</td>
<td>107</td>
</tr>
<tr>
<td>Thurin et al. (2004)</td>
<td>Age &lt; 36 years, &lt; 2 previous cycles, &gt; 1 good embryo</td>
<td>661</td>
</tr>
<tr>
<td>Martikainen et al. (2001)</td>
<td>&gt; 3 good embryos, Some age selection, &lt; 2 previous cycles</td>
<td>144</td>
</tr>
<tr>
<td>Gerris et al. (1999)</td>
<td>1st treatment, Age &lt; 34 years, &gt; 1 good embryo</td>
<td>53</td>
</tr>
</tbody>
</table>

*Sixteen cycles were Day 5 blastocyst transfers.

Discussion

The analysis here has further quantified the substantial loss in live birth resulting from a SET when compared with a DET, showing that the loss is consistent across all patients. We have explored a number of approaches to selecting appropriate patients for SET, demonstrating that a number of these can ameliorate the loss. If we take a complete cycle perspective with cryopreservation, we have suggested it is potentially possible for SET to outperform DET.
Strengths and weaknesses of this study

Based on a large multi-centre cohort from routine clinical care, we have been able to predict outcomes for both SET and DET in the same patients. The results obtained are consistent with the clinical trial data, albeit at a somewhat lower overall LBR, reflecting the fact that these are patients from routine care rather than selected for trials. Where increased use of SET has been introduced as a national policy, success rates have not decreased significantly. However, this was on a background of steadily improving outcomes, and it is reasonable to assume that the rates would have continued to improve and been higher with DET than with the SET policy (Tiitinen and Gissler, 2004; Gordts et al., 2005; Karlstrom and Bergh, 2007).

The data here come from a cohort of 2000–2005. Other than an increase in the proportion of SET, practice for these Day 2–3 embryo transfers has not changed appreciably in the intervening period. However, there has been an increase in the use of blastocyst transfer (Khalaf et al., 2008), which is not considered here and is an option that needs careful evaluation. Extended embryo culture can improve the success rate in the initial fresh transfer (Blake et al., 2005) but reduces the availability of embryos for later frozen transfers. As a result of this, it is unclear whether the initial increase in success outweighs the subsequent losses, and there is little if any evidence that the overall cumulative LBR is higher using blastocyst transfer (Guerif et al., 2009).

We believe that the scenarios presented here are representative of current clinical practice, although practice will vary between centres. While outcomes for individual fresh embryo transfers can be computed directly from the models, results for multi-transfer scenarios require the use of simulation methods and a number of assumptions and extrapolation from other data sources. There is a good deal of uncertainty around the frozen transfers, with less reliable data. Thus, we based the simulations involving frozen transfers on a range of plausible values rather than the actual data estimates.

Clinical implications

At least in European countries, there is widespread acceptance of the need to reduce the number of twin births in order to reduce the incidence of adverse outcomes for mother and baby (Cutting et al., 2008). Some evidence is emerging that the reduction of twin rates related to the adoption of SET policies can lead to reductions in the incidence of cerebral palsy (Kallen et al., 2010a).

It is clear that in any individual embryo-transfer procedure, the use of SET will lower the chances of a successful outcome relative to DET. The results here suggest that this is true for all patients who have two good-quality embryos, with the loss showing little dependence on patient characteristics. From a population or clinical perspective this loss can be mitigated by selection of patients for SET, and a number of realistic strategies can reduce the loss in LBR by about half. However from an individual patient perspective, all patients who receive SET have a lower chance of success in that transfer cycle, but do of course avoid the risks associated with twin pregnancy.

This picture is, however, transformed if we consider the transfer of all the embryos created over a series of fresh and frozen embryo-transfer procedures. Then we find that it is possible for SET to have an LBR similar to that of DET, for all patients. Nevertheless, SET does require more transfer procedures, which increases the burden on patients and service providers. These simulations suggest that universal SET at the early-cleavage stage could be a viable option, providing that funding arrangements allow the complete cycles, similar to those existing in Belgium. The model parameters at which rough equality for SET/DET is achieved are close to those seen in the best of the centres in the study, and so are likely to be achievable, although further work is needed to confirm this. This is an intuitive result, as for each embryo-transfer procedure, there is a possibility that the recipient may not be receptive or that the transfer procedure may fail. Thus, there may well be an advantage in spreading the risk over a number of transfer cycles, which has to be offset against the losses in freezing and thawing. The breakeven point is sensitive to the details of freezing policy, embryo quality and practice. We do assume that embryos are thawed in rather smaller batches than is often used in current practice. Freezing policies need to ensure that embryos are not thawed or discarded unnecessarily, possibly at the expense of a small number of cancelled cycles. Newer techniques such as vitrification (Balaban et al., 2008) may improve freezing performance further. There is a need for careful observational studies and randomized trials to optimize freezing techniques.

Patient perspectives

Patients undergoing IVF treatment have been shown to have a preference for twins (Gleicher et al., 1995; Goldfarb et al., 1996; Pinborg et al., 2003; Porter and Bhattacharya, 2005) and our own work supports this view (Roberts et al., 2010b). Twins are seen as a positive and not a negative outcome. Consistent with other studies (Blennborn et al., 2005; Porter and Bhattacharya, 2005; Glazebrook et al., 2007), in our own qualitative work (Roberts et al., 2010b), patients emphasized the emotional, physical and for some, financial, burden of treatment. Given this, twins represent a ready-made family, which would negate the need for further treatment. Others have shown that people tend to downplay risk across a range of events, and often provide an inaccurate judgement of personal risk (Lek and Bishop, 1995). This ‘trade off’ between twin pregnancy and multiple cycles appeared to be used to cognitively appraise a difficult treatment decision and re-enforce the preference for DET. Recent work has shown that the need for ‘treatment success’ dominates any future
concerns about the risks to babies of twin pregnancy and birth (Scotland et al., 2007).

In our work (Roberts et al., 2010b), the drive towards SET was viewed by many patients as a government strategy to restrict and divert resources from expensive IVF treatment to other areas. This provoked a sense of unfairness among participants. There was limited knowledge and understanding regarding the use of frozen embryos with scepticism about the thawing process and embryo survival. If patients are to be encouraged in the uptake of SET to reduce multiple pregnancy and birth, a more comprehensive understanding of frozen embryo transfer is required to make this an attractive option.

In order to reduce twin rates, clinics will either need to impose a policy and/or persuade their patients that SET is an acceptable treatment option. Clinicians need to be aware of patient views and beliefs so that they can work with patients collaboratively in making treatment choices. There is a need to develop more targeted interventions to increase patient knowledge and understanding. In addition, patients require reassurance that the move towards a SET policy is for both their own and their babies’ benefit, and not driven by external factors, such as resource rationing or financial considerations.

Conclusion

For any transfer, SET has about a one-third lower LBR relative to DET. This can be partially mitigated by appropriate patient and treatment cycle selection, with several realistic policies performing similarly. However, all patients receiving SET would have a higher chance of successful treatment in that cycle if they received DET. In contrast, if we consider complete cycles with embryo cryopreservation, it is possible for repeat SET to produce more live births per egg retrieval than repeat DET. The good outcome with repeat SET is dependent on a high rate of successful cryopreservation and preservation of embryo viability, and more work is required to understand how this should be optimized. Patients consider the additional treatments required under SET to be burdensome and this will be a significant obstacle to its increased use.

Ethical approval

The project received a favourable opinion from the South Manchester Research Ethics Committee (ref 06/Q1403/254 and 06/Q1403/255).

Authors’ roles

S.A.R. conceived and led the project, designed the study, designed and contributed to the analyses and wrote the paper. L.M. led on the design and analysis of the qualitative work and contributed to the design of the simulation studies and the manuscript. W.M.H. collated the data sets and performed the statistical analyses. A.V. contributed to the statistical design, analysis and the manuscript. A.R. advised on the project and contributed to the clinical interpretation of the results and the manuscript. B.A.L. was involved in the design of the project and reviewed the manuscript. The toward SET collaboration: provided data and provided advice throughout the project. D.R.B. provided clinical input to the design and conduct of the study and contributed to the manuscript.

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