MANCHESTER 1824

The University of Manchester

towardSET?
Predictive models & Patient perspectives

PROTOCOL

Towards single embryo transfer. Modelling clinical outcomes of potential treatment choices using multiple data sources: predictive models and patient perspectives.

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1. Background

1.1. Existing research

Single Embryo Transfer (SET): Elective SET (eSET) has been widely advocated on the basis that it reduces the number of multiple pregnancies, and the consequent risk to the mother and offspring (e.g. Pinborg 2005). Many cohort studies (reviewed in Bergh, 2005; Gerris, 2005) suggest that on a per transfer cycle basis SET does indeed reduce twinning rates compared to double embryo transfer (DET) , but that this is associated with a reduced success rate. This has been confirmed in a limited number of relatively small randomised trials (Pinborg, 2005), although no good quality randomised data are yet available (Pandian *et al,* 2005). The subsequent replacement of single thawed embryos increases the pregnancy rate per episode of IVF on a cumulative basis (e.g. Lukassen *et al*, 2005). Strategies to implement SET are likely to require evaluation across multiple cycles of embryo transfer, and there are currently trials ongoing comparing a single fresh cycle of DET to two cycles of SET one fresh and one utilising a frozen embryo from the first cycle (e.g. the ECOSSE trial led by Dr Bhattacharya, Aberdeen, see http://www.bertarelli-foundation.ch/index.php/BF/entry/efficacy_and_cost_effectiveness_of_selective_single_embryo_transfer_ecosse/)

Clinician and patient perspectives: There is widespread agreement amongst IVF clinicians that, at least in good prognosis patients, policies to prevent multiple pregnancies, including twin pregnancies, are to be preferred. Many recommendations have been made to increase the proportion of eSET and this is now legally prescribed in Sweden (reviewed in Bergh, 2005). However many centres in the United Kingdom are reluctant to adopt policies that might lead to a reduction in pregnancy rates, particularly in the format published by the HFEA, and particularly where patients pay directly for the treatment. The format of outcome data published by the HFEA allows centres to be rated in "league tables". This is widely seen as being of commercial value to centres in the top echelons; SET is more popular where the treatments are publicly funded as in northern Europe. For example in Manchester within the NHS at St Mary's Hospital (SMH) the SET rate is 30%, whilst in the private sector at Manchester Fertility Services (MFS) it is 10%. The definition of treatment success rate is crucial here (e.g. Bhattacharya & Templeton, 2004) and some consensus on a measure that takes the whole treatment programme into account, as well as the patient population, is urgently required.

The HFEA currently use the "live birth rate per treatment cycle commenced" as the measure of success. A treatment cycle commences with ovarian stimulation. This denominator is difficult to validate as many of these "commenced cycles" are cancelled before egg recovery and the data are only reported after the cycle has been completed. It may be preferable to define success as seen by the patients, e.g. the cumulative live birth rate per egg recovery procedure, following replacement of the fresh and all the frozen embryos. This may more accurately reflect the efficiency of the unit and the patients' expectation of treatment (surgical operation for egg recovery). The use of a per-cycle endpoint rather than a per-patient endpoint also invites invalid analyses and comparisons based on assumptions of independence between cycles.

In contrast to clinical opinion, a number of studies have shown that patients themselves do not favour eSET and see twins as a positive, not a negative outcome (Blennborn *et al*, 2005; Gleicher *et al*, 1995; Goldfarb *et al*, 1996; Murray *et al*, 2004; Pinborg *et al*, 2003; Porter & Bhattacharya, 2005) and this perception is not easily altered (Murray *et al*, 2004). Given this dichotomy of views between patients and clinicians it is crucial that patients are involved in the decision-making process, and in the formulation of national and institutional policy. The appropriate policy may differ depending on the source of funding.

In order for patients to make informed choices, accurate and relevant information is essential to this process (Deyo, 2001). However, a recent study which compared standard information alone, with additional information sheet on twin pregnancy or discussion, the extra information did not affect couples attitudes to a hypothetical policy of eSET (Murray *et*

al., 2004). Therefore, further research is required to understand the specific information needs of this patient group, and the timing of this information. Future policy initiatives around eSET, and engagement in clinical trials, are reliant on patient commitment and trials require a certain degree of equipoise.

Research has shown that with careful counselling and appropriate additional treatment cycles to maintain the overall pregnancy rates, trials of eSET can be successfully undertaken: in the UK there is an ongoing multi-centre trial, the UK ECOSSE trial, mentioned above. This trial has been limited to clinics which share common embryo selection and freezing policies and so the results will not be able to be extrapolated to all clinics. The level of patient acceptance of this trial is not known. Within SMH the rate of elective replacement of single embryos is increasing for patients at high risk of a multiple pregnancy, e.g. young women with a history of conception.

Embryo selection: The ability to select a "top quality" embryo for transfer is crucial to the success of eSET (e.g. De Neubourg *et al*, 2004). Selection is normally made on morphological grounds, with different scoring systems in use in different centres. There is considerable interest in selection criteria (e.g. Ebner *et al*, 2003), and in alternative markers to morphology (e.g. Brison *et al,* 2004). Our own Manchester-Leeds-York collaboration (following on from Brison *et al,* 2004) is currently conducting a multicentre study of the use of amino-acid profiles in the spent culture medium as a marker of embryo quality. Treatment policies on the length of culture of fertilised embryos, the day of transfer, and the use of cryopreservation differ between centres, thus different centres will have differing numbers of embryos at different stages from which to select. To our knowledge no comparative or modelling studies have been undertaken which consider the impact of different cryopreservation/selection policies and it is crucial to capture this in any assessment of the impact of SET.

Prognostic factors: Retrospective studies have identified a number of patient, embryo and treatment factors that are associated with treatment success. Female age and previous reproductive success are the principal maternal predictors, along with basal FSH levels and duration of infertility (e.g. HFEA, 2005; Templeton *et al*, 1996; Kupka *et al,* 2003). Embryo quality is clearly important, as assessed by morphology (Ebner *et al,* 2003). Smoking, both maternal and paternal, is associated with poor outcomes, but the evidence for other lifestyle factors is weak (Klonoff-Cohen, 2005).

Economics: Few studies looking specifically at eSET from the economic perspective have been reported (reviewed in Bergh, 2005). From a societal perspective, these indicate that the savings in health costs associated with twin pregnancies may offset the direct additional costs of the repeat SET cycles required to maintain the same take home baby rate. However in many cases the direct costs of treatment are borne by the patients, whilst the costs associated with multiple births are (in the UK) met within the NHS. A recent publication (Ledger *et al*, 2006) has studied the impact of multiple births from a UK perspective. In addition there are less readily quantifiable costs associated with a potential requirement for extra treatment cycles per baby in eSET.

What's been done already: Six RCTs have been undertaken comparing forms of SET with DET in, generally, good prognosis patients (Gardner *et al*, 2004; Gerris *et al*, 1999; Lukassen *et al,* 2005; Martikainen *et al*, 2001; Thurin *et al*, 2004; Van Montfoort *et al*, 2006; reviewed in Bergh, 2005). SET alone gives poorer outcomes in terms of live birth rate per implantation cycle but reduces the incidence of twins to a rate comparable with natural pregnancies. In one small randomised trial, SET with two episodes of embryo replacement is associated with a similar live birth rate as DET but with a significant reduction in the number of multiple births (Lukassen *et al* 2005, see also Thurin *et al* 2004). There is a lack of large, good-quality trials comparing practical policies. Cohort studies (reviewed in Bergh, 2005; Gerris, 2005) show similar conclusions, but these are harder to interpret as the patients undergoing SET are selected by a combination of the clinician and the couple. Most of these analyses use simple per treatment cycle endpoints and fail to account for the correlations between cycles. Clinical experience in Sweden and elsewhere (reviewed in Bergh, 2005) suggests that a legal prescription towards eSET has led to an increased use of SET whilst maintaining success rates and dramatically reducing twin rates.

Inference from patient cohorts: Three approaches have been used:

1. Estimation of pregnancy or live birth rates arising from SET v DET, with varying definitions and patient subsets (e.g. Gerris *et al*, 2002; Martikainen *et al*, 2004; De Neubourg *et al*, 2002; Tiitinen *et al*, 2003; Van Montfoort *et al*, 2005; Vilska *et al*, 1999). These suffer from inbuilt biases in the selection of patients for SET. In many retrospective datasets it is difficult to know the true reason for SET. In some studies this is "patient choice", in others it is perceived clinical need (patients for whom twin pregnancies are contraindicated) or some combination of the two.

2. Logistic regression of success rates and twin rates in DET to determine factors that predict a high twinning probability (e.g. Strandell *et al*, 2000). These methods potentially identify high risk groups, but give no information on the potential outcomes if SET were used.

3. Explicit modelling of embryo and recipient (uterine) effects. Within this framework models derived from DET data can be used to predict SET outcomes. The one published example of this (EU) approach, Hunault *et al* (2002) use the Zhou & Weinberg (1998) model, but attributes all the prognostic parameters to the embryo, fitting a constant uterine receptivity (U). Our own work attributes the predictive factors to their natural level and includes both embryo and recipient covariates. These models have the advantage that they allow predictions of SET outcomes from multiple embryo transfer data, avoiding the selection issues in the retrospective comparative studies. The models make other assumptions, particularly around the independence of the embryo and uterine effects, although there is no evidence that these assumptions are inappropriate.

In all these types of analysis considerable care and expertise is required in conducting and interpreting the analyses, not only because of the inbuilt biases of the observational data, but also to account appropriately for the non-trivial correlation structures between multiple egg-collection and replacement cycles from the same individuals and from centre and cohort effects. Such considerations are rare in the analyses published to date.

1.2. Our own work

We have undertaken methodological work (Roberts, 2006) on models that incorporate embryo-level effects – a non-trivial matter as it is often not known which of the transferred embryos implanted and gave rise to a pregnancy. These are generalisations of the Spiers EU model (Spiers *et al*,1983). We are currently using the EU approach to analyse our Manchester data and investigate the potential for SET. This work has demonstrated a number of prognostic factors and indicated that embryo quality may be rather more complex a predictor than has previously been assumed. From these models we have been able to obtain some preliminary predictions as to the potential success and twinning rates under a range of choices of SET v DET. These analyses suggest that regardless of the prognosis at that time, a decision based on a single transfer cycle is always likely to involve trading off a significant drop in the chance of having a baby against the relatively small risk associated with a significant chance of having twins. We tentatively conclude that the SET v DET decision needs to be based on a multi-cycle perspective, either including further replacement cycles using frozen embryos, or further egg-collection cycles, but that larger and more diverse datasets are required with both fresh and frozen replacement cycles in order to draw firm conclusions. We have a methodological interest in developing these approaches further, particularly to incorporate random effects in both the embryo and uterine response. Preliminary analysis of the Manchester cohort using maximum likelihood methodology indicates that these inter-cycle correlations between fresh cycles are significant if the simple EU model is used, but that they become undetectable if models incorporating the couple-level covariates are used. We have also investigated these models in a Bayesian Markov-Chain Monte-Carlo (MCMC) framework, and here we find (as have e.g. Dukic & Hogan, 2002; Natarajan & McCulloch, 1998) that convergence is poor and these MCMC approaches require careful application.

2. Planned investigation

2.1. Research objectives

1) To collate high-quality cohort data from a series of individual treatment centres to be considered alongside HFEA data and data from an ongoing embryo selection study. [Quarters 1-2]

2) To develop predictive models from each of the three data sources for (a) twinning probabilities in patients treated with DET from fresh or frozen embryos, (b) success probabilities in couples receiving SET and (c) potential singleton and twin rates if couples had been offered SET. In each case to consider the full range of potentially prognostic factors associated with the couple and the available embryos, including age, fertility history, cause of infertility and embryo quality (the latter is not available for the HFEA data). [Q3-5]

3) To understand, through qualitative work, the patient perspective on these choices as they travel through the treatment process. [Q1-4]

4) To involve couples in developing patient-relevant outcome measures for IVF treatment programmes and a range of potential choices and treatment options for consideration. [Q1-8]

5) To consider a number of potential outcomes and denominators (including, but not limited to: per couple, per embryo transfer cycle, per stimulated cycle started, per completed cycle) from a clinical and patient perspective, and to predict these for potential treatment scenarios based on proposals in the literature, and developed with patients and clinicians. [Q6-7]

6) To use the modelling results to investigate with patients the acceptability of the scenarios and the changes in public policy required to make SET acceptable. [Q7-8]

7) To suggest appropriate randomised controlled trials to test the effectiveness of the most favourable policies. [Q8]

2.2. Research methods

The decision whether to have single or double embryo transfer is currently made by the individual couple following advice and counselling from the clinical staff. Thus in the present UK situation it is important to understand the patient perspective on twins and SET. Even if one were to advocate a policy of compulsory SET, in formulating such a policy the patients' views would need to be considered. Thus we propose an inter-disciplinary approach in which quantitative retrospective cohort studies and predictive modelling are embedded within qualitative studies of patient perspectives in an integrated manner. The various components are described below.

2.3. Initial literature review

We will review the literature to (1) identify studies where SET has been compared to DET, both randomised trials and cohort studies (recently reviewed in Gerris, 2005 and Bergh, 2005); (2) identify prognostic factors to be included in the models; (3) identify series where published data are available with sufficient detail to be used in model verification and (4) identify strategies for the use of SET in clinical practice and the obstacles to their adoption.

2.4. Retrospective Cohort studies (objectives 1 & 2)

We will undertake a series of linked cohort studies to determine factors associated with

success and twin rates in SET and DET. Our collaboration will include the full spectrum of patient settings including NHS-funded patients attending a centre offering only NHS treatment (SMH), private patients attending a fully-private clinic (MFS) and NHS-funded, fee-paying NHS patients and self funded (private) patients within NHS clinics (Leeds, Birmingham, Liverpool, Newcastle). The centres included cover a range of policies on SET, embryo selection and freezing. By considering the full range of patients, we ensure that our results can be generalised to patients treated within the NHS in the likelihood that future policy developments, such as the recent NICE recommendation, lead to changes in the demographic and clinical characteristics of NHS patients.
Specifically we will collate data from the following sources:

1. Data from the national HFEA register. This provides outcome data on each embryo-replacement cycle conducted in the UK, with a useful, but not exhaustive set of patient, partner and cycle factors. However this dataset contains no embryo-level data. The data are anonymised, but records relating to the same couples are linked. For these analyses we would initially propose to use a 2000-2005 cohort, extending this if required. There are issues about data quality in such databases, but the Historic Audit project (due to be completed early 2006) will at least ensure the quality of the data in cycles which generated a pregnancy. [Collaborator: Charles Lister]

2. A collection of single-centre information-rich datasets with embryo quality measures on all transferred embryos. We will extract a cohort with full outcome data for treatments completed in the 2000-2005 timeframe. We currently have 6 centres who have indicated they are willing to provide the necessary data, covering a range of practice and funding models, and which provide sufficient data for the purposes.
   a. We are currently analysing a large cohort (1998-2003) from the St Mary's Assisted Conception Unit in Manchester - currently 1989 cycles from 1388 patients, with detailed treatment, prognostic and outcome data. We will update these data to give approximately 2400 cycles. These are entirely NHS-funded patients with a high rate of elective SET. [Daniel Brison and Brian Lieberman]
   b. Similar data are available from the Manchester Fertility Services clinic, with identical data recording and database. These are entirely private patients. Approximately 2000 cycles. [Brian Lieberman and Daniel Brison]

   Both SMH and MFS have a Day 1 embryo freezing policy which means that maximum of 4 embryos are available for selection of one (SET) or two (DET) for transfer. The following 4 collaborating centres are all NHS centres of excellence with a mixture of NHS and fee-paying patients. They all have an embryo freezing policy which allows all embryos to be available for transfer, in contrast to SMH and MFS.

   c. Leeds (LGI). Again using the same database system. Approximately 4000 cycles [Collaborator: Tony Rutherford]
   d. Liverpool Women's Hospital. Approximately 4000 cycles. [Collaborator: Steve Troup]
   e. Newcastle Fertility Unit. NHS and fee-paying patients. Approximately 2500 cycles. [Collaborator: Mary Herbert]
   f. Birmingham Women's Hospital, NHS and fee-paying patients. Approximately 2400 cycles. [Collaborator: Sue Avery]

3. We are currently conducting a prospective study of the use of amino acid profiles for the prediction of embryo viability. Recruitment is scheduled to complete by August 2006 and full outcome data will be available during the course of this study. We will have 400 DET plus >100 SET with detailed embryo-level data, patient data and a controlled clinical study setting, including external monitoring and validation of the data collection.

From these data we will develop a series of statistical models for the various outcome measures (success, twins, per transfer cycle, per egg collection cycles etc.) as a function of the patient, embryo and treatment characteristics (see statistical methods section below).

This phase of the study will produce a series of statistical models relating outcome (singleton, twins) to prognostic indicators for fresh and frozen embryo transfer across multiple treatment cycles. These models will identify prognostic factors leading to high risk of twins and high chance of success, and provide the basis for the consideration of the role of SET.

2.5. Patient perspectives (objectives 3 & 4)

In this phase of the study we will undertake in-depth qualitative interviews with couples who are in the process of undergoing IVF treatment. The aim is to explore the patient perspective of treatment choices as they travel through the treatment process. Therefore, interviews will take place at 3 key decision-making stages: a) waiting list; b) after the first information meeting and clinical appointment (pre-treatment) and c) after the second cycle of treatment. This latter group will allow for views to be assessed once the outcome of an initial treatment cycle is known and after the opportunity to reflect on the choices through a second treatment cycle. Approximately 5 to 10 couples per stage will be invited to take part in this study. Purposive sampling techniques will be employed to ensure maximum diversity of sample to include different female ages, parity, duration of infertility and source of funding (which is related to the number of treatment cycles which the couple receive). Couples will be invited to take part in this study, and once consent has been obtained, interviews will take place in the setting (clinic/home) of their choice.

Specifically we will plan:

a. To assess couples' knowledge and views on embryo transfer and twin birth prior to treatment, after counselling and post-treatment.
b. To explore the potential facilitators and barriers to eSET.
c. Evaluate the patient perspectives on the decision-making process during key stages of the treatment journey, including consideration of measures of success and attitudes to twin births.
d. Determine the level of involvement couples would prefer in the decision making process regarding treatment choices.
e. To establish at what stage (pre-treatment) information regarding treatment choices about eSET should be presented, and in what format.
f. To explore couples attitudes to research, in particular, their understandings of randomisation.

This phase of the study will improve our knowledge of information giving strategies relevant for this patient group. Furthermore, a more in-depth understanding of the decision-making process that underlies the decision for SET and the factors likely to be important if a policy of encouraging (or mandating) eSET were to be considered. Outcomes which are of importance to the patients will be identified, and attitudes to research design will be explored. The differing perspectives of patients, and their interaction with health professionals, will be understood in a more rigorous manner, and a range of potential strategies for the use of eSET established.

2.6. Predictive Modelling (objectives 5 & 6)

Based on our survey of the literature and the qualitative work above we will identify a limited number of potential treatment policies and choices involving the use of SET, based on a patient perspective of the whole treatment course. These will include, but not be limited to, single transfer cycle choices, single DET versus two cycles of SET (with the second fresh or frozen), and will include a range of couple prognoses. We will use the models developed above to predict the outcomes of the various scenarios for the whole range of prognostic factors, with estimates of their reliability. This predictive modelling will encompass both direct prediction from the models and the use of model parameters (and their associated uncertainties) to make predictions for treatment policies not contained within the source datasets. In developing the models we will take care to consider the correlations between cycles, and to assess the errors in the prediction, validating against both internal and

external data where these exist (see statistical methods below). Crucially, these will include consideration of the effect of different embryo selection/freezing practices (i.e. the maximum number of embryos available from which the one or two transferred are selected; see above), ignored by most previous studies. Specifically we will model the impact of SET in centres (such as SMH and MFS) in which only a limited number of embryos are available for selection for transfer (with remaining embryos being previously frozen) in comparison to centres in which all embryos generated are available for selection.

We will establish three focus groups (two NHS, one private sector) of AC patients and partners who have been through the process and will present to them the results from the modelling process. This methodology has been successfully employed to explore sensitive issues (Kitzinger, 1995; 1990). A convenience sample of couples who have undergone assisted conception treatment will be invited to participate in a structured focus group. In order to facilitate maximum group interaction groups consisting of between 6 to 8 couples per group will be sought. This size is considered ideal when dealing with knowledgeable groups (Krueger, 1994). Once informed consent has been obtained focus groups will be conducted within the clinic setting, and travel expenses will be reimbursed. Initially, two groups (one NHS; one private sector) will be conducted to obtain a range of potential viewpoints. Following a general discussion about the various treatment options, a selection of scenarios from the statistical modelling will be presented to the groups in a user friendly format. The scenarios may include, for example, a comparison of outcomes on a single-cycle basis for couples with varying prognosis and a similar comparison of potential outcomes for choice between single cycle DET or two-cycle (fresh+frozen) SET, again for good and poor prognosis. The groups will be asked to score the scenarios on a range of key variables using a Likert scale. The findings from these two focus groups will be collated and then verified with a third focus group (NHS). This will allow for issues raised in the first two groups, which may not have been on the research agenda, to be explored in more detail. We will explore the responses to the results, and determine potential barriers to the proposed solutions. This may lead to alternative strategies to be investigated.

This final phase of the study will yield a range of potential policy decisions, their potential outcomes in terms of success and twin rates along with an understanding of their acceptability to patients and the factors that may impede or encourage their implementation.

2.7. Towards randomised controlled trials (objective 7)

Ultimately any proposed treatment strategies will need to be tested in rigorous randomised controlled trials (RCTs). Based on the knowledge gained from these studies we will suggest a design or designs for such trials, defining patient populations, treatments and endpoints. Such a trial would also include a rigorous health economic assessment. The qualitative element of this project will establish existing views of patients regarding RCTs, and these can be incorporated into the trial design. Furthermore, the findings will enable the production of accurate and targeted patient information.

2.8. Proposed sample size

Formal sample size computations are not appropriate here as the aim is to develop predictive models, not to formally test hypotheses. Experience and heuristic arguments suggest that datasets in excess of 10,000 subjects will be required for this exercise. Rules of thumb for reliable predictive modelling suggest 10-20 events per considered variable. We expect to have around 40 potential variables which with a success rate of 20% would imply a minimum data set of 4000 independent cycles, around 8000 patients given that many patients have multiple cycles and we wish to look at multi-cycle endpoints. The sample size is in practice determined by the need to have a representative set of centres and a long enough time span to capture treatment histories along with computational feasibility, and is well in excess of the minimum numbers above.

3. Study Conduct

3.1. Clinical Data Collation

Data collation will be an iterative process involving close liaison between the project team and contributing centres and overseen by the SAB. Three datasets will be created as detailed in (§2.4)

3.1.1. Routine data

Detailed discussions will take place between the project team and each of the 7 contributing centres listed above (§2.4 1&2). Following these discussions a data collation plan will be drafted detailing

1. The minimal dataset to be collected from every site
2. Any additional site-specific data
3. The time period to be collected for each site (may vary due to logistical issues – e.g. changes of data collection processes/database software)
4. The details of the anonymisation and identification of repeat treatments from the same individuals (see §3.1.3 below)
5. The method of data transfer (email or disk)
6. The formats of each variable and the post-processing necessary to make these consistent across sites
7. Descriptions of the embryo grading systems in use at each site and day of transfer
8. Data checking/validity algorithms
9. The structure of the final analysis database and the processing needed to get each centre's data into the database. This will require careful consideration of the hierarchical structure of the data.

This document will be circulated to the SAB for comments and formal approval (either at a face-to-face meeting or via email).

An initial data extraction (maybe of just a sample of the data) and transfer to the project team will then take place and the processes outlined above tested and any issues resolved and any amendments discussed and approved.

The full data extraction will then take place and the complete database assembled and verified. Such iteration as necessary will take place to resolve any data validity issues. Preliminary logistic regression models will be fitted to the assembled datasets using the minimal set of covariates defined in (a) above and any outliers and discrepancies resolved in consultation with the centres. After this stage the database will be locked.

3.1.2. Trial data

The trial data (§2.4 item 3) will be available to the study investigators as DB and SAR are CI and Study statistician respectively on that trial. These data are being collated by Hesperion as per the protocol for that trial and who will be providing an anonymised data set for analysis.

3.1.3. Anonymisation

No personally-identifiable clinical data shall be sent to or retained by the investigators. All data will be anonymised by the contributing centre. Each patient will be given a unique identifier, *maintaining the same identifier across multiple cycles for the same patient*. The appropriate form of the identifier will be determined separately for each centre depending on the practicalities of data extraction and database capabilities. The numbers allocated

must be such that no one outside the contributing centre can identify the patients, thus a hospital number will not be acceptable, but a reference internal to the database holding the data (eg row number in a patient identifier table) would be suitable. All personal identifiers will be removed prior to transmission of the data to the Chief Investigator for analysis. It is permitted that the centre retains a *temporary* copy of the allocated numbers cross-referenced to patient/cycle identifiers so that problems with the data can be identified and resolved. Any such temporary lists will be destroyed at the end of the data extraction/validation phase of the project.

3.2. Patient Perspective Interviews

Note: The descriptions below refer to "couple" as the unit of investigation. This is not intended to imply that in all cases there will be two partners of opposite sex, and there is no exclusion criterion that refers to the patients relationships. If there are potential participants where the relationship is not that of the majority, or where only one partner wishes to be involved, then these should be handled sensitively and with appropriate tailoring of the invitation letters and information sheets as needed for the individual circumstances.

3.2.1. Recruitment process

Purposive sampling techniques will be employed to ensure maximum diversity of sample to include different female ages, parity, duration of infertility and source of funding (which is related to the number of treatment cycles which the couple receive). The qualitative researcher (LMcG) will draw up criteria for the patient characteristics in consultation with clinical investigators. Additionally, patients will be made aware of the study at their 'waiting list' meeting (all potential patients are invited to attend this session prior to commencement of treatment, at which they are given basic information about their treatment). For patients who have not had their initial meeting contact will be by letter, later stage patients will be approached in person by the Study Research Nurse in the clinic setting.

Interviews will take place with patients at 3 key decision-making stages: a) waiting list; b) after the first information meeting and clinical appointment (pre-treatment) and c) after the second cycle of treatment (this time point is to capture the views of "experienced" patients, but as some couples will only receive a single cycle patients who have completed treatment with a single cycle may be included in this group).

a) waiting list patients will be identified by the Research Nurse (who is part of the clinical team) from the waiting list. The Research Nurse will obtain minimal contact details of the selected patients on the waiting list from clinic staff. The Research Nurse will then mail an INVITATION PACK which will include:

1. An invitation letter inviting couples to take part in this study.

2. An information sheet explaining the rationale of the study, the design, and how it will be conducted and managed. The principles of confidentiality, anonymity and privacy have been explained in the participant information sheet.

3. A form to be completed by couples and returned to the researcher stating whether they want to take part in the study, or not, and how they can be contacted. The form will allow for couples to indicate that they would prefer to discuss the study further, with the researcher, prior to making a decision as to whether to take part or not.

4. A stamped addressed envelope will be provided to return the forms stating their decision about participating to the researcher.

All couples who receive an INVITATION PACK will be requested to complete and return a signed form if they are willing to participate in this study.

Those who reply will be contacted directly by the qualitative researcher (LMcG) by

telephone/email to discuss the study further. Any queries or concerns may be addressed at this point. An appointment will be made for a mutually convenient time and place if they wish to take part in an interview. Those couples who state that they do not wish to take part, or do not return the form, will not be contacted again about the study.

b) after the first information meeting and clinical appointment (pre-treatment)and c) after the second cycle of treatment:

At the next relevant clinic visit patients will be approached directly by the Research Nurse (who is a member of the clinical team). The Research Nurse will have been fully briefed by the researcher (LMcG) regarding the aims and objectives of the study. This will enable them to identify suitable participants at these 2 key treatment phases, so that they can introduce the study to patients. Potential participants will be given the information sheet and letter of invitation (on Hospital notepaper) by the nurse, who will explain the study verbally and answer any questions. Those who are willing will be contacted by telephone a few days later to ascertain if they are interested. Patients and partners will be given as long as the wish to consider participation. Those who express an interest to the Research Nurse will be asked to give contact details so that the research team can make an appointment for interview. The qualitative investigator (LMcG). will contact the potential participant by phone to answer any questions and make the practical arrangements for the interview. If the potential participants require further time to consider participation then a second phone call will be agreed. Formal written consent will be recorded at the interview after an additional explanation of the study and a further opportunity to opt out.

All participants:

Immediately prior to the interview the consent will be discussed and signed individual consent forms will be obtained. Couples will be reassured regarding confidentiality and anonymity. A copy of the consent form will be given to the participants. A short demographic questionnaire will be completed prior to the interview which will ask only about those characteristics of importance to this study.

3.2.2. Interview Conduct

In-depth exploratory interviews, employing the conversational style, will be conducted with couples at the three key treatment stages of interest (waiting list; after the first information meeting and clinical appointment; and after the second cycle of treatment). Interviews will be conducted in a setting of the couple's choice (either home or clinic). Travel expenses and refreshments will be provided for those couples who opt for a clinic setting. All interviews will be taped, with permission, and transcribed prior to analysis.

The interview will begin by asking couples to describe their individual experiences, including their interactions with the health care system. In effect, the couples will be asked to tell their "stories". Should topics not emerge that are relevant to the study the interviewer (LMcG) will refer to the interview schedule (Appendix 3) and guide the respondents accordingly. In keeping with qualitative research the interviews will be analysed in stages. Early interviews will analysed and the data used to inform the format of later interviews. So when couples introduce information/areas which are new (i.e. not recorded in the literature or previously known to the researcher) these will be incorporated in to later interviews.

All interviews will be coded by number and anonymised. All interviews will be transcribed verbatim by secretarial staff who are used to dealing with material of a medical/research nature.

3.3. Patient Focus Groups

3.3.1. Recruitment process

This will follow the process for the interviews (§3.2.1) and all patients will be first

approached by the Study Research Nurse in the clinic or by letter from a member of the Clinical care team.

3.3.2. Focus Group Conduct

Couples who express a wish to take part will be contacted by telephone or email (method of contact following their expressed preference) by LmcG and offered a choice of times and dates when the group meeting will take place. Immediately prior to the focus group the consent will be discussed and signed consent forms will obtained. Couples will be reassured regarding confidentiality and anonymity. A copy of the consent form will be given to the participants at this time.

Patients and their partners will be allocated to one of three focus groups (two NHS; one private sector) consisting of six to eight couples per group. Couples will be invited to attend these small group discussions at a suitable venue (St. Mary's Hospital – NHS; Manchester Fertility Services – private sector); the necessary maps and bus routes will be provided. Travel expenses will be reimbursed. The aim is to make these meetings as relaxed and informal as possible. Couples who attend will be greeted warmly and light refreshments will be provided.

The researcher (LMcG) will act as group facilitator. An assistant (research associate) will maintain the tape recording equipment and take the necessary field notes. The facilitator will encourage the group to discuss general areas of interest concerning assisted conception treatment to open the session. Gradually, the facilitator will adopt a more interventionist style (Kitzinger, 1995), steering the debate towards topics of interest to the study (see Appendix 4). It is anticipated that these group sessions will last one to two hours. On completion, the couples will be thanked for contributing their time and effort to the project. All those couples who take part will be sent a resume of the main findings from the focus groups.

All group interviews will be coded by number and anonymised. All group interviews will be transcribed verbatim by secretarial staff who are used to dealing with material of a medical/research nature.

3.4. Recording and transcript retention

Interviews and focus groups will be recorded on two portable recorders (digital and standard audio-tape as back-up). After each interview the data will be stored immediately either on the University server (password protected) for digital material or stored in a locked cabinet (audio-tapes) on University premises. The qualitative researcher (LMcG) will act as principal custodian for the interview data. Analysed data from the study will be stored for five years.

3.5. Confidentiality

Interviews will be transcribed a soon as possible and all personal names/identifiers will be changed. Thus, after each interview the anonymised recorded data will be emailed to the transcriber. When the interview has been transcribed, this will be emailed back to either the researcher and she will check the transcription back against the recorded interview and make any amendments. The transcriber will be asked to delete her copy of the recorded interview from her computer. All digital recordings/tapes will be destroyed on completion of the study.

All data sets will be assigned a unique code and will only be identified this way in any ensuing reports and publications. Verbatim material reported by participants will be anonymised. This will ensure that selected quotes cannot be linked to individual study participants.

4. Data Analysis

4.1. Statistical analysis

Within each of the cohorts we will use hierarchical logistic regression to develop predictive models for success per transfer cycle for patients receiving SET and DET from both fresh and frozen embryos. Within the DET cohorts we will develop similar models for twinning rates. These models will use aggregated embryo data and be applied to all three data series. Models will be developed which (a) include all potentially prognostic factors as determined from the literature and (b) include factors found to be predictive in the current series using statistical model selection based on the Akaike Information Criterion.

For the single centre and AAP datasets where we have embryo-level data we will utilise the EU model (Speirs *et al*, 1983) and develop models for outcome per cycle which explicitly include recipient and embryo effects (Roberts, 2006; Zhou & Weinberg, 1998). Again models will be developed which (a) include all potentially prognostic factors as determined from the literature along with (centre specific) measures of embryo development and quality and (b) include factors found to be predictive in the current series using statistical model selection based on the Akaike Information Criterion. These models can be fitted using maximum likelihood and (more generally) using an MCMC approach and WinBugs. We have software written in R (R Development Core Team, 2005) which can fit the EU models by direct maximisation of the likelihood and which can include a couple-level random effect. We also have WinBugs (http://www.mrc-bsu.cam.ac.uk/bugs/winbugs/contents.shtml) code to fit these models by MCMC methodology, although this latter approach does suffer from slow convergence (Dukic & Hogan, 2002; Natarajan & McCulloch 1998).

We will consider the full range of potential predictive factors, as far as the datasets will allow, and will take care that each variable is included in an appropriate manner. For instance our work with the Manchester data has shown that both age and embryo quality require appropriate semi-parametric methods (that analysis used cubic splines) to capture the complexities of the relationships.

Essential to the modelling process will be the interaction between the statisticians, embryologist and clinicians. Regular discussion between the three groups will ensure that the models remain clinically relevant and will continually inform the modelling process. Statistical model selection methods will be employed, but these will not be used blindly, but in a supervised way informed by clinical knowledge. This interaction has proved essential in obtaining useful models of the Manchester data.

We will give careful consideration to the hierarchical nature of data and within-cycle and within-patient correlations (Ecochard & Clayton, 1998). For the HFEA data, and for combined analyses of the single-centre datasets, this will require consideration of centre effects using appropriate random effect models.

We will also give consideration to potentially more appropriate outcome measures which are derivable from the datasets and which take into account the whole treatment programme. Explicitly we intend to include, where possible, live birth per egg collection and cumulative pregnancy rate from patients with cycles early in each clinic cohort. Due consideration of the (both left and right) censoring of the treatment histories will inform the definition, utilisation and analysis of these endpoints, principally by ensuring rigorous definition of the endpoints and selection of appropriate analysis datasets.

From these models we will be able to predict outcomes for a range of treatment scenarios. In particular the EU models will allow prediction of SET outcomes for those patients who received DET. These predictions will include direct predictions from the models, and also predictions for treatment regimens beyond those encompassed within the datasets. For the latter we will use the parameter estimates from the models, including the estimates of inter-cycle correlations to estimate outcomes for multi-cycle treatment programmes. We will utilise a number of approaches to determine the accuracy of the prediction, both statistical

(bootstrap, cross-validation and training/validation set methods) and internal (comparisons between the data series) and external (comparison with published trial data) comparisons.

4.2. Qualitative Analysis

Interviews and focus groups will be taped and transcribed *verbatim.* Data will be managed using specialist software for qualitative data (NVIVO). The data will be analysed using the principles of Framework analysis (Ritchie & Spencer, 1994). There are five key stages in the analysis: 1) *Familiarisation* – the transcripts will be read thoroughly by all researchers to identify key themes. 2) *Developing a thematic framework* - a framework was developed that was applied to the transcripts. Following discussions with co-researchers, this framework will then be expanded and refined. 3) *Indexing* – themes and emerging subthemes are labelled and indexed. 4) *Charting* – framework involves devising a series of thematic charts or matrices. 5) *Mapping and interpretation* – the aim is to bring out the key characteristics and map and interpret the data as a whole. A benefit of using Framework analysis is that strategies and recommendations for practice and policy may be elicited at this stage.

4.3. Outcome measures

The primary outcomes will be live birth and twin births. An important consideration in the modelling is the appropriate aggregated outcome measure, or measures, for a course of treatment. The live births per cycle started, egg collection or transfer cycle whilst convenient, are not appropriate measures by which to compare treatment scenarios which may involve multiple cycles. Part of the qualitative work proposed is to identify appropriate aggregated outcome measures which encompass the patient, clinical and societal perspectives of successful treatment.

5. Project Governance and Ethics

5.1. Ethical arrangements

Approval from an NHS Research Ethics Committee will be sought through the COREC system once funding is confirmed, and before the project commences. All the data are available from routine clinic or HFEA records, and there is no need to contact individual patients. All data will be anonymised on extraction and provided to the researchers without any personal identifiers. As such we believe it is unnecessary, as well as impractical to seek individual patient consent, and indeed it would probably be considered unethical to re-contact patients unnecessarily. We have obtained ethics approval to analyse the Manchester data on this basis. The qualitatitive work will involve patients, and written informed consent will be obtained. This work has the potential to raise distressing topics and provoke conflict. We will work closely with the subfertility counsellors to minimise and mitigate such events, and the interviewer has the necessary experience and training to deal with such issues as may arise.

5.2. Research Governance

Research governance will be overseen by the University of Manchester. PS120906

5.2.1. Management Group

The project will be managed by a Management Group comprising the named investigators, the RA statistician, the Study Nurse involved in recruitment and the qualitative research assistant. This will meet monthly to oversee the project.

5.2.2. Advisory Group

In addition we will create an Advisory Group (AG) drawn from the wider collaborators and including a patient representative. The AG will meet at the start of the project to approve the protocol and at approximately 6 month intervals to provide guidance and a wider clinical perspective. See appendix 5 for membership. This group will be chaired initially by the Chief Investigator, but may elect its own chair at the first meeting. The format of the meetings will be agreed by the Group at the first meeting. The first meeting will be face-to-face and will provide an opportunity to meet the research team.

5.2.3. Contracts

The investigators all have contracts with both the University and the Central Manchester Trust and similar arrangements will be made for all those working on the project.

5.2.4. Publication

All manuscripts and conference presentations must be approved by the Management Group before submission. Authorship will be determined by that group following the Vancouver Group guidelines (www.icmje.org) Specifically we note:

- Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.

- Acquisition of funding, collection of data, or general supervision of the research

group, alone, does not justify authorship.

All collaborators contributing data will be acknowledged by name and affiliation in all publications that use that data, and contributors will have the chance to review the manuscript before submission.

Unless otherwise indicated (e.g. for methodological or other sub-studies) the default is that all 5 investigators and the RA will be listed as authors of all publications together with anyone else who has made a significant intellectual input to the manuscript.

The primary publication will be the HTA monograph which will be authored by the named investigators and the RA and reviewed by the SAG.

6. Project timetable and milestones

We propose a 4-month lead in time from confirmation of funding to the formal project start. During this time we will obtain ethical and Trust R&D approvals and appoint the Research Associate. We anticipate that this will lead to a start date of 1/1/07, but this could be earlier or later if required by the contractual process. The project is then expected to last for 2 years.

	Year 1				Year 2			
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8
Literature review	x	x	x	x				
Collate and clean datasets	x	x						
Preliminary analyses			x					
Logistic modelling			x	x				
EU modelling				x	x			
Scenario modelling					x	x	x	
Patient/clinician perspectives	x	x	x	x				
Analysis of qualitative data			x	x	x	x		
Patient consultations			x	x	x	x	x	x
Write up								x

Key milestones:

Project start: Ethical approval obtained and Research Associate in post
6 months: Single centre datasets collated and validated
12 months: Patient interview work on perspectives completed
12 months: Logistic modelling of SET & DET cohorts
15 months: EU modelling of single-centre data
18 months: Patient/clinician perspectives analysis complete
21 months: Analytic work complete
24 months: Write up complete

7. Collaborators

Jenny Dunlop, SMH counselling service

Tony Rutherford (Leeds)

Steve Troup (Liverpool)

Mary Herbert/Jane Stewart (Newcastle)

Sue Avery (Birmingham)

Charles Lister on behalf of the HFEA.

8. References

Bergh C. Single embryo transfer: a mini-review. *Hum Reprod* 2005; **20**: 323-327.

Bhattacharya S, Templeton A. What is the most relevant standard of success in assisted reproduction? Redefining success in the context of elective single embryo transfer: evidence, intuition and financial reality. *Hum Reprod* 2004; **19**(9):1939-42.

Blennborn M, Nilsson S, Hillervik C, and Hellberg D. The couple's decision-making in IVF: one or two embryos at transfer? *Hum Reprod* 2005; **20**: 1292-1297.

Brison DR, Houghton FD, Falconer D, Roberts SA, Hawkhead JA, Humperson PG, Lieberman BA, and Leese HJ. Selection of viable embryos in IVF by non-invasive measurement of amino acid turnover. *Hum Reprod* 2004; **19**: 2319-2324.

De Neubourg D, Gerris J, Mangelschots K, Van Royen E, Vercruyssen M, Elseviers M. Single top quality embryo transfer as a model for prediction of early pregnancy outcome. *Hum Reprod* 2004; **19**(6):1476-9.

De Neubourg D, Mangelschots K, Van Royen E, Vercruyssen M, Ryckaert G, Valkenburg M, Barudy-Vasquez J, and Gerris J. Impact of patients' choice for single embryo transfer of a top quality embryo versus double embryo transfer in the first IVF/ICSI cycle. *Hum Reprod* 2002; **17**, 2621-2625.

Deyo, RA. A key medical decision maker: the patient. *BMJ* 2001; **323**: 466-467.

Dukic V, Hogan JW. A hierarchical Bayesian approach to modeling embryo implantation following in vitro fertilization. *Biostatistics* 2002; **3**(3):361-77.

Ebner T, Moser M, Sommergruber M, and Tews G. Selection based on morphological assessment of oocytes and embryos at different stages of preimplantation development: a review. *Human Reproduction Update* 2003; **9**:251-262.

Ecochard R and Clayton DG. Multi-level modelling of conception in artificial insemination by donor. *Stat Med* 1998; **17**:1137-1156.

Gardner DK, Surrey E, Minjarez D, Leitz A, Stevens J, and Schoolcraft WB. Single blastocyst transfer: a prospective randomized trial. *Fertil Steril* 2004; **81**:551-555.

Gerris J, De Neubourg D, Mangelschots K, Van Royen E, Van de Meerssche M, and Valkenburg M. Prevention of twin pregnancy after in-vitro fertilization or intracytoplasmic sperm injection based on strict embryo criteria: a prospective randomized clinical trial. *Hum Reprod* 1999; **14**:2581-2587.

Gerris J, De Neubourg D, Mangelschots K, Van Royen E, Vercruyssen M, Barudy-Vasquez J, Valkenburg M, and Ryckaert G. Elective single day 3 embryo transfer halves the twinning rate without decrease in the ongoing pregnancy rate of an IVF/ICSI programme. *Hum Reprod* 2002; **17**: 2626-2631.

Gerris JM. Single embryo transfer and IVF/ICSI outcome: a balanced appraisal. *Hum Reprod Update* 2005; **11**:105-121.

Gleicher N, Campbell DP, Chan CL, Karande V, Rao R, Balin M, and Pratt D. The desire for multiple births in couples with infertility problems contradicts present practice patterns. *Hum Reprod* 1995; **10**, 1079-1084.

Goldfarb J, Kinzer DJ, Boyle M, and Kurit D. Attitudes of in vitro fertilization and intrauterine insemination couples toward multiple gestation pregnancy and multifetal pregnancy reduction. *Fertil Steril* 1996; **65**:815-820.

HFEA Guide to Infertility and Directory of Clinics 2005/06. UK Human fertilisation and

Embryology Authority 2005;
http://www.hfea.gov.uk/ForPatients/Archivedinformation/PatientsGuidetoInfertility

Hunault CC, Eijkemans MJ, Pieters MH, te Velde ER, Habbema JD, Fauser BC, and Macklon NS. A prediction model for selecting patients undergoing in vitro fertilization for elective single embryo transfer. *Fertil Steril* 2002; **77**:725-732.

Kitzinger J. Recalling the pain: incest survivors experiences of obstetrics and gynaecology. *Nursing Times* 1990; **86**:38-40.

Kitzinger J. Qualitative research: Introducing focus groups. *BMJ* 1995; **311**:299-302.

Klonoff-Cohen H. Female and male lifestyle habits and IVF: what is known and unknown. *Hum Reprod Update* 2005; **11**(2):179-203.

Kruegar RA. *Focus groups: A practical guide for applied research*. 1994. (2nd ed.) Newbury Park. CA. Sage.

Kupka MS, Dorn C, Richter O, Felberbaum R, van der Ven H. Impact of reproductive history on in vitro fertilization and intracytoplasmic sperm injection outcome: evidence from the German IVF Registry. *Fertil Steril* 2003; **80**(3):508-16.

Ledger WL, Anumba D, Marlow N, Thomas CM, Wilson EC; Cost of Multiple Births Study Group (COMBS Group). Cost of Multiple Births Study (COMBS) group. *British Journal of Obstetrics and Gynaecology* 2006; **113**(1):21-5.

Lukassen HG, Braat DD, Wetzels AM, Zielhuis GA, Adang EM, Scheenjes E, and Kremer JA. Two cycles with single embryo transfer versus one cycle with double embryo transfer: a randomized controlled trial. *Hum Reprod* 2005; **20**: 702-708.

McGowan L. Luker K, Chew-Graham C, Creed F. "How do you explain a pain that can't be see?" The narratives of women with chronic pelvic pain and their disengagement with the diagnostic cycle. *Brit J of Health Psychol* 2006; in press.

Martikainen H, Orava M, Lakkakorpi J, and Tuomivaara L. Day 2 elective single embryo transfer in clinical practice: better outcome in ICSI cycles. *Hum Reprod* 2004; **19**:1364-1366.

Martikainen H, Tiitinen A, Tomas C, Tapanainen J, Orava M, Tuomivaara L, Vilska S, Hyden-Granskog C, and Hovatta O. One versus two embryo transfer after IVF and ICSI: a randomized study. *Hum Reprod* 2001; **16**:1900-1903.

Murray S, Shetty A, Rattray A, Taylor V, and Bhattacharya S. A randomized comparison of alternative methods of information provision on the acceptability of elective single embryo transfer. *Hum Reprod* 2004; **19**:911-916.

Natarajan R, McCulloch CE. Gibbs sampling with diffuse proper priors: A valid approach to data-driven inference? *Journal of Comutational and Graphical Statistics* 1998; **7**(3): 267-277.

Pandian Z, Bhattacharya S, Ozturk O, Serour GI, Templeton A. Number of embryos for transfer following in-vitro fertilisation or intra-cytoplasmic sperm injection. *Cochrane Database Syst Rev* 2004;(4):CD003416.

Pinborg A, Loft A, Schmidt L, and Andersen AN. Attitudes of IVF/ICSI-twin mothers towards twins and single embryo transfer. *Hum Reprod* 2003; **18**: 621-627.

Pinborg A. IVF/ICSI twin pregnancies: risks and prevention. *Human Reproduction Update* 2005; **11**:575-593.

Porter M and Bhattacharya S. Investigation of staff and patients' opinions of a proposed trial of elective single embryo transfer. *Hum Reprod* 2005; **20**: 2523-2530.

R Development Core Team. R: A language and environment for statistical computing. *R Foundation for Statistical Computing* 2005; Vienna, Austria. http://www.R-project.org.

Ritchie J, Spencer L. Qualitative data analysis in applied policy research. In: Bryman and Burgess (eds) *Analysing qualitative data*.1994 Routledge; London.

Roberts SA. Embryo-level Models for Assisted Conception data with embryo-specific covariates. *Stat Med* 2006; In press.

Speirs AL, Lopata A, Gronow MJ, Kellow GN, and Johnston WIH. Analysis of the Benefits and Risks of Multiple Embryo Transfer. *Fertility and Sterility* 1983; **39**:468-471.

Strandell A, Bergh C, and Lundin K. Selection of patients suitable for one-embryo transfer may reduce the rate of multiple births by half without impairment of overall birth rates. *Hum Reprod* 2000; **15**:2520-2525.

Templeton A, Morris JK, Parslow W. Factors that affect outcome of in-vitro fertilisation treatment. *Lancet* 1996; **348**(9039):1402-6.

Thurin A, Hausken J, Hillensjo T, Jablonowska B, Pinborg A, Strandell A, and Bergh C. Elective single-embryo transfer versus double-embryo transfer in in vitro fertilization. *N Engl J Med* 2004; **351**: 2392-2402.

Tiitinen A, Unkila-Kallio L, Halttunen M, and Hyden-Granskog C. Impact of elective single embryo transfer on the twin pregnancy rate. *Hum Reprod* 2003; **18**: 1449-1453.

Vail A, Gardener E. Common statistical errors in the design and analysis of subfertility trials. *Hum Reprod* 2003; **18**:1000-4.

Van Montfoort AP, Dumoulin JC, Land JA, Coonen E, Derhaag JG, and Evers JL. Elective single embryo transfer (eSET) policy in the first three IVF/ICSI treatment cycles. *Hum Reprod* 2005; **20:** 433-436.

Van Montfoort AP, Fiddelers AA, Janssen JM, Derhaag JG, Dirksen CD, Dunselman GA, Land JA, Geraedts JP, Evers JL, Dumoulin JC. In unselected patients, elective single embryo transfer prevents all multiples, but results in significantly lower pregnancy rates compared with double embryo transfer: a randomized controlled trial. *Hum Reprod* 2006; **21**(2):338-43.

Vilska S, Tiitinen A, Hyden-Granskog C, and Hovatta O. Elective transfer of one embryo results in an acceptable pregnancy rate and eliminates the risk of multiple birth. *Hum Reprod* 1999; **14**: 2392-2395.

Zhou H and Weinberg CR. Evaluating effects of exposures on embryo viability and uterine receptivity in in vitro fertilization. *Stat Med* 1998; **17**: 1601-1612.

Appendix I Interview recruitment documents

- Invitation letter
- Return Slip
- PIS for interviews
- consent form

On Hospital Paper

Address: <insert>

Date: <insert>

Dear <insert>,

Re: **Patient perspectives on single embryo transfer**

We would like to invite you to take part in a study which aims to explore patient views on single embryo transfer. This project is a joint venture between the Department of Reproductive Medicine, St. Mary's Hospital and the University of Manchester and will be conducted by a research team which includes statisticians and doctors.

Currently UK policy limits the number of embryos transferred to two, but many doctors advocate single embryo transfer, due to the increased risks of twin pregnancies. It is clear to us that couples undergoing IVF treatment may not share the same perspective on the risk and benefits as doctors, and we wish to understand what patients feel so that the results of our research will reflect your wishes. Hence we are conducting this study to attempt to understand patients' perspectives on the choices you and your doctor have to make. An information sheet about the proposed study is enclosed.

At the same time the statisticians are conducting a research project involving complex statistical modelling techniques to investigate the potential outcomes of various possible policies towards the increased use of single embryo transfer in IVF treatments. We are investigating the potential impact of a move to single embryo transfer in various circumstances on success rates and numbers of twins.

The researcher conducting this part of the project is Linda McGowan who is a Lecturer/Researcher specialising in women's health at the University of Manchester

We recognise that decisions about this kind of treatment also involve your partner. Therefore, participation in this study can involve both you and your partner taking part in an interview about your views of the important aspects of your treatment and decisions concerning your treatment. The interview should last no longer than **1 hour** and confidentiality will be ensured.

We hope you will agree to participate. If you require further information regarding the study, please do not hesitate to contact Linda McGowan (Tel: 0161 275 5345; email:

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linda.mcgowan@mancheter.ac.uk) If you are interested in participation please let us know using the response form and the stamped addressed envelope enclosed and Linda will contact you.

Yours sincerely

[to be signed by a member of the clinical team]

Please return in the envelope provided

towardSET?
Predictive models &
Patient perspectives

Patient perspectives on single embryo transfer study

I am willing to be contacted by the researcher about taking part in this research study: ☐

I am not willing to be contacted by the researcher about taking part in this research ☐

Name _____

Address: _____

_____

_____

Telephone Number: _____

Please tick (✓) as appropriate:
I **can** be contacted by **telephone** to arrange a suitable time and place to be interviewed ☐

I **can** be contacted by **email** to arrange suitable time and place to be interviewed ☐
(*please write email address below*)

_____

_____

Thank you for your help, please return the enclosed form in the stamped address envelope provided and return to: ***Dr Linda McGowan, Research Nurse, School of Nursing, Midwifery & Health Visiting, University of Manchester, Coupland Building III, Oxford Road, Manchester M13 9PL(Tel: 0161 275 5345, email: linda.mcgowan@mancheter.ac.uk)***

MANCHESTER 1824

The University of Manchester

towardSET?
Predictive models & Patient perspectives

Patient perspectives on Single Embryo Transfer

Participant Information Sheet for Patient Interviews

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Please retain this sheet for your information if you choose to participate.

What is the purpose of the study?

We are conducting a research project involving complex statistical modelling techniques to investigate the potential outcomes of various possible policies towards the increased use of single embryo transfer in IVF treatments. We are investigating the potential impact of a move to single embryo transfer in various circumstances on success rates and numbers of twins. Currently UK policy limits the number of embryos transferred to two, but many doctors advocate single embryo transfer, due to the increased risks of twin pregnancies. It is clear to us that couples undergoing IVF treatment may not share the same perspective on the risk and benefits as doctors, and we wish to understand what patients feel so that the results of our research will reflect your wishes. Hence we are conducting this study to attempt to understand patients' perspectives on the choices you and your doctor have to make.

Why have I been chosen?

We are seeking the views of a wide spread of couples undergoing IVF treatment, at different stages in their treatment journey. You have been chosen simply because you are at a particular stage at this point in time.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

We will contact you by telephone to arrange a suitable time and place for the interview. This can be on Clinic premises or we can arrange to meet in your own home or on University premises. One of the researchers, Linda McGowan, will conduct the interviews. The interviews are intended to be relaxed and conversational in nature. Each interview will begin by asking you and your partner to describe your individual treatment experiences, including your interactions with the health care system. If topics are not covered that are of interest to the

researcher, she will ask some supplementary questions. The interviews should take between 30 minutes to one hour.

The interviews will be recorded so we can remember exactly what was said, these recordings will be transcribed and anonymised so that you will not be personally identified in any analysis and reporting of the study. We may use anonymous quotes from your discussions to illustrate the points you were making.

We will reimburse you for any travel expenses you incur.

What do I have to do?

Depending on your stage of treatment you will becontacted either by letter, or by the Research Nurse in the clinic, and given information about the study. You will have the opportunity to ask questions at this time. If you decide that you would like to take part in this study, you will be asked to provide contact details. The researcher (Linda McGowan) who will be conducting the interviews will then contact you by phone to discuss the study further, and to answer any other queries you may have. If you are still willing to participate a suitable time, date and location (home or clinic) for the interview will be arranged. You will be asked to sign a formal written consent form just before the interview begins.

A second phase of the study will involve focus groups to discuss with the researchers the range of treatment options they should explore and to consider preliminary results of their work. If you would be interested in being part of that study then let us know at the interview. Other than this possibility your participation will be just the single interview.

What are the possible disadvantages and benefits of taking part?

We recognise that talking about issues related to your treatment could raise emotional issues, which you may find upsetting. However, the person you will be talking to (Linda McGowan, a nurse & psychologist, is a very experienced researcher who is used to dealing with issues of a sensitive nature. Should issues arise that cannot be dealt with in the context of the interview, the researcher as the support of one of the subferility counselling staff (Jenny Dunlop) at St. Mary's Hospital with whom she can seek advice. On the other hand you may find it helpful to talk about your treatment experiences to someone outside the clinical setting. Your input will make a valuable contribution to the development of the wider research programme and potentially influence NHS policy in this area.

What will happen if I don't want to carry on with the study?

You may withdraw from the study at any stage. If you change your mind and do not wish to be interviewed please inform Linda McGowan. Your treatment will not be affected in any way.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (see contact numbers below). If you remain unhappy and wish to complain formally, you can do this through the Hospital

Complaints Procedure. Details can be obtained from [Insert details for Central Manchester Trust or MFS as appropriate]

In the event that something does go wrong and you are harmed during the research study the University offers a no fault compensation scheme.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential and all procedures for handling, processing, storage and destruction of their data will be compliant with the Data Protection Act 1998.

The interviews will be recorded and transcribed for analysis, and following transcription the recordings will be destroyed. After transcription all names and other personal identifiers will be removed and you will be identified only by gender and a code number. Quotations may be used as part of the report of this research, but only quotations that cannot be attributed to an individual will be used.

What will happen to the results of the research study?

The results of this study will be published by the Department of Health as a "HTA monograph" which we expect will be available sometime in 2009 and which will be available via the Web or from the researchers. If you would like a summary of the results of this study please let the research team know and we will let you have a copy when it is available. Additionally results will appear in the scientific literature. You will not be personally identified in any publication.

Who is organising and funding the research?

This research is being conducted by researchers at the University of Manchester as part of a wider study which is funded by the Department of Health (Health Technology Assessment programme).

Who has reviewed the study?

This study was given a favourable ethical opinion by the [Insert REC]

Contact Details:

Linda McGowan is the lead researcher for this study and can be contacted via details below. **Steve Roberts** is the **Chief investigator** for the overall project and can be contacted via 0161 275 5764

Thank you for taking time to read this sheet.

Contact details for research interviewer:
Dr Linda McGowan
Faculty of Medical and Human Sciences

School of Nursing, Midwifery & Social Work
Coupland III Building
University of Manchester
Oxford Road
Manchester
M13 9PL

Phone: 0161 275 5345
Fax: 0161 275 7566
email: linda.mcgowan@manchester.ac.uk

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Predictive models & Patient perspectives

Interview CONSENT FORM

Title of Project: Patient perspectives on Single Embryo Transfer

Name of Researcher: Linda McGowan

Please initial box

1. I confirm that I have read and understand the information sheet dated 10.11.06 (*version 1*) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I agree that the interview may be recorded. ☐

4. I agree to the publication of anonymous quotations from the interview. ☐

5. I agree to take part in the above study. ☐

Name of Participant	Signature	Date
Name of Participant	Signature	Date
Name of Person taking consent	Signature	Date
Researcher	Signature	Date

When completed: 1 copy for patient; 1 (original) for researcher file

Appendix ii Focus group recruitment documents

- Invitation letter
- Return Slip
- PIS for focus groups
- Consent form

On Hospital notepaper

Address <insert>

Date <insert>

Dear <insert>,

Re: **Patient perspectives on single embryo transfer**

We would like to invite you to take part in a study which aims to explore patient views on single embryo transfer. This project is a joint venture between the Department of Reproductive Medicine, St. Mary's Hospital and the University of Manchester and will be conducted by a research team which includes statisticians and doctors.

Currently UK policy limits the number of embryos transferred to two, but many doctors advocate single embryo transfer, due to the increased risks of twin pregnancies. It is clear to us that couples undergoing IVF treatment may not share the same perspective on the risk and benefits as doctors, and we wish to understand what patients feel so that the results of our research will reflect your wishes. Hence we are conducting this study to attempt to understand patients' perspectives on the choices you and your doctor have to make. An information sheet about the proposed study is enclosed.

At the same time the statisticians are conducting a research project involving complex statistical modelling techniques to investigate the potential outcomes of various possible policies towards the increased use of single embryo transfer in IVF treatments. We are investigating the potential impact of a move to single embryo transfer in various circumstances on success rates and numbers of twins

The researcher conducting this part of the project is Linda McGowan who is a Lecturer/Researcher specialising in women's health at the University of Manchester.

We recognise that decisions about this kind of treatment also involve your partner. Therefore, participation in this study can involve you and your partner taking part in taking part in one focus group. This is where a group of couples who have undergone similar treatment would come together to discuss their views about the important aspects of IVF treatment and decisions concerning such treatment The focus group should last no longer than **2 hours**, and confidentiality will be ensured. Refreshments will be freely available throughout.

We hope you will agree to participate. If you require further information regarding the study, please do not hesitate to contact Linda McGowan (Tel: 0161 275 5345; email: linda.mcgowan@mancheter.ac.uk) If you are interested in participation please let us know

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using the response form and the stamped addressed envelope enclosed and Linda will contact you.

Yours sincerely

[to be signed by a member of the clinical team]

Please return in the envelope provided

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Patient perspectives on single embryo transfer study

I am willing to be contacted by the researcher about taking part in this research study: ☐

I am not willing to be contacted by the researcher about taking part in this research ☐

Name _____

Address: _____

_____

_____

Telephone Number: _____

Please tick (✓) as appropriate:
I **can** be contacted by **telephone** to arrange a suitable time and place to be interviewed ☐

I **can** be contacted by **email** to arrange suitable time and place to be interviewed ☐
(*please write email address below*)

_____

_____

Thank you for your help, please return the enclosed form in the stamped address envelope provided and return to: ***Dr Linda McGowan, Research Nurse, School of Nursing, Midwifery & Health Visiting, University of Manchester, Coupland Building III, Oxford Road, Manchester M13 9PL(Tel: 0161 275 5345, email: linda.mcgowan@mancheter.ac.uk)***

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Patient perspectives on Single Embryo Transfer

Participant Information Sheet for Patient Focus Groups

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Please retain this sheet for your information if you choose to participate.

What is the purpose of the study?

We are conducting a research project involving complex statistical modelling techniques to investigate the potential outcomes of various possible policies towards the increased use of single embryo transfer in IVF treatments. We are investigating the potential impact of a move to single embryo transfer in various circumstances on success rates and numbers of twins. Currently UK policy limits the number of embryos transferred to two, but many doctors advocate single embryo transfer, due to the increased risks of twin pregnancies. It is clear to us that couples undergoing IVF treatment may not share the same perspective on the risk and benefits as doctors, and we wish to understand what patients feel so that the results of our research will reflect your wishes. Hence we are conducting this study to attempt to understand patients' perspectives on the choices you and your doctor have to make.

Why have I been chosen?

We are looking to see what factors might affect couples choices regarding IVF treatments, therefore, we are seeking the views of a wide spread group of couples have undergone this treatment process. You have been chosen simply because you have experienced this kind of treatment.

Do I have to take part?

No. It is up to you to decide whether or not to take part. If you do, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?

We will contact you by telephone to arrange a suitable time and place for the focus group meeting. We will then meet at the location for the group meeting, in this case, Hospital premises. One of the researchers, Linda McGowan, will conduct the focus groups. She will be assisted by a research associate who will maintain the recording equipment, and make may relevant notes so that we do not miss anything important. The focus groups are intended to be

relaxed and conversational in nature, and refreshments will be served. Each focus group will begin by asking you and your partner to discuss your treatment experiences. If topics are not covered that are of interest to the researcher, she will ask some supplementary questions. She will also show you some scenarios taken from the preliminary results of the statistical modelling. These will be presented in a user friendly format and will be used to aid the discussion about treatment choices. The idea behind this is to see that if you had been aware of these factors would this have affected your choice of treatment. You will be asked to rate these scenarios according to your preferences, there are no right or wrong answers, we are simply interested in your individual views. This will enable the researchers to identify which range of treatment options they should explore in future work. The focus group interviews should take between one to two hours.

The focus group interviews will be recorded so we can remember exactly what was said, these recordings will be transcribed and anonymised so that you will not be personally identified in any analysis and reporting of the study. We may use anonymous quotes from your discussions to illustrate the points you were making.

We will reimburse you for any travel expenses you incur.

What do I have to do?

Depending on your stage of treatment you will be contacted either by letter, or by the Research Nurse in the clinic, and given information about the study. You will have the opportunity to ask questions at this time. If you decide that you would like to take part in this study, you will be asked to provide contact details. The researcher (Linda McGowan) who will be conducting the focus groups will then contact you by phone to discuss the study further, and to answer any other queries you may have. If you are still willing to participate a suitable time, date and location (home or clinic) for the focus group will be arranged. You will be asked to sign a formal written consent form just before the focus group begins.

What are the possible disadvantages and benefits of taking part?

We recognise that talking about issues related to your treatment could raise emotional issues, which you may find upsetting. However, the person you will be talking to (Linda McGowan, a nurse & psychologist, is a very experienced researcher who is used to dealing with issues of a sensitive nature. Should issues arise that cannot be dealt with in the context of the focus group interview, the researcher as the support of one of the subferility counselling staff (Jenny Dunlop) at St. Mary's Hospital with whom she can seek advice. On the other hand you may find it helpful to talk about your treatment experiences to someone outside the clinical setting, and to share your experiences others who have undergone a similar treatment programme. Your input will make a valuable contribution to the development of the wider research programme and potentially influence NHS policy in this area.

What will happen if I don't want to carry on with the study?

You may withdraw from the study at any stage. If you change your mind and do not wish to be interviewed please inform Linda McGowan. Your treatment will not be affected in any way.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (see contact numbers below). If you remain unhappy and wish to complain formally, you can do this through the Hospital Complaints Procedure. Details can be obtained [Insert centre-specific details]

In the event that something does go wrong and you are harmed during the research study the University offers a no fault compensation scheme.

Will my taking part in this study be kept confidential?

All information which is collected about you during the course of the research will be kept strictly confidential and all procedures for handling, processing, storage and destruction of their data will be compliant with the Data Protection Act 1998.

The focus group interviews will be recorded and transcribed for analysis, and following transcription the recordings will be destroyed. After transcription all names and other personal identifiers will be removed and you will be identified only by gender and a code number. Quotations may be used as part of the report of this research, but only quotations that cannot be attributed to an individual will be used.

What will happen to the results of the research study?

The results of this study will be published by the Department of Health as a "HTA monograph" which we expect will be available sometime in 2009 and which will be available via the Web or from the researchers. If you would like a summary of the results of this study please let the research team know and we will let you have a copy when it is available. Additionally results will appear in the scientific literature. You will not be personally identified in any publication.

Who is organising and funding the research?

This research is being conducted by researchers at the University of Manchester as part of a wider study which is funded by the Department of Health (Health Technology Assessment programme).

Who has reviewed the study?

This study was given a favourable ethical opinion by the[Insert REC].

Contact Details:

Linda McGowan is the lead researcher for this study and can be contacted via details below. **Steve Roberts** is the **Chief investigator** for the overall project and can be contacted via 0161 275 5764

Thank you for taking time to read this sheet.

Contact details for researcher conducting the focus group interviewers:
Dr Linda McGowan
Faculty of Medical and Human Sciences
School of Nursing, Midwifery & Social Work
Coupland III Building
University of Manchester
Oxford Road
Manchester
M13 9PL

Phone: 0161 275 5345
Fax: 0161 275 7566
email: linda.mcgowan@manchester.ac.uk

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Focus Group CONSENT FORM

Title of Project: Patient perspectives on Single Embryo Transfer

Name of Researcher: Linda McGowan

Please initial box

1. I confirm that I have read and understand the information sheet dated ..... (version .....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I agree that the group may be recorded. ☐

4. I agree to the publication of anonymous quotations from the group. ☐

5. I agree to take part in the above study. ☐

Name of Participant	Signature	Date
Name of Person taking consent	Signature	Date
Researcher	Signature	Date

When completed: 1 copy for patient; 1 (original) for researcher file

Appendix III Interview Topic Guide

LREC reference number: 06/Q1403/255

Interview Group Topic Guide v1.1 (04/05/2007)

INTERVIEW GUIDE

General introduction

As we explained in our letter current UK policy limits the number of embryos transferred to two, but many doctors advocate single embryo transfer, due to the increased risks of twin pregnancies. It is clear to us that couples undergoing IVF treatment may not share the same perspective on the risk and benefits as doctors, and we wish to understand what patients feel so that the results of our research will reflect your wishes. We are conducting this interview study to attempt to understand patients' perspectives on the choices you and your doctor have to make. This interview will be taped with your permission.

Short demographics questions:
How old are you?
How old is your partner?
Do you have any children in your family?
How long have you been seeking treatment for infertility?
How is your treatment going to be funded?

TOPIC AREAS TO BE DISCUSSED:

- **Could you describe to me your general experience of treatment to date?**

  Ascertain stage of treatment
  Length of time on waiting list
  Number of treatments to date
  General experiences of treatment – explore the perceptions of a 'good' outcome?

- **Discuss differences between SET and DET, and explore current knowledge regarding treatment:**

  Explore attitudes to twin pregnancy
  Assess current understanding of risks associated with multiple births
  Explore facilitators to eSET
  Explore barriers to eSET
  Discuss eSET policy

LREC reference number: 06/Q1403/255

- **We recognise that during your treatment you will have a number of important decisions to make. We would like to know how involved you would like to be with your doctor in making these decisions?**

  Explore preferences for involvement in treatment decision making:
  - medically led
  - patient led
  - collaborative model

  Ascertain if the preferred model of decision-making should be different at the different treatment stages

- **Clearly, having clear and accurate information about the treatment process is essential. We would like to know what kind of information you would find most helpful?**

  Explore information preferences:
  Ascertain information needs at key treatment stages

  - what kind of information is most helpful
  - timing of information
  - amount of information
  - format of information

- **In medical research a common method of finding out which is the best form of treatment is to conduct a randomised controlled trial. Have you heard of this kind of research***? (if not, explain briefly)*

  Ascertain current understanding of randomised controlled trials
  Explore views of being randomised to receive one or two embryos

- **Is there anything I have missed in our discussion that you consider to be important?**

Appendix IV Focus group topic guide

FOCUS GROUP TOPIC GUIDE

TOPIC AREAS TO BE DISCUSSED:

- **Open with a general discussion about the various treatment options e.g.**
  Single embryo transfer (SET) – 1 cycle
  Double embryo transfer (DET) – 1 cycle
  SET with fresh embryo – 1 cycle
  SET with frozen embryo 1 cycle
  SET with one fresh & one frozen embryo – 2 cycle

- **Present a selection of scenarios from the results of the statistical modelling:**
  Provide instructions to the group (*via a Powerpoint slide*). This will cover:
  What the terms mean
  How to read the scenarios
  How to rate the scenarios
  How long they have got to read and rate the scenarios
  Any questions before we begin?

- **Explore general views, opinions and attitudes to the various scenarios presented:**
  Did you find the exercise easy to do?
  Was this a useful exercise?
  Did any of you change your mind about a treatment after reading these scenarios?
  How do you feel about a policy that encourages SET?
  Is this different to how you felt before?
  What would be your preferred treatment option?
  What do you think is a 'good' treatment outcome?

- **Discuss the concept of randomised controlled trials**
  What is your understanding of randomised controlled trials?
  How you would feel about being 'randomised' to receive either one or two embryos?
  If you were invited to take part in such a trial would you agree to participate?

- **Is there anything I have missed in our discussion that you consider to be important?**

Appendix V AG membership and role

A1.1 Membership

Jenny Dunlop,
Tony Rutherford (Leeds)
Steve Troup (Liverpool)
Jane Stewart (Newcastle)
Sue Avery (Birmingham).
Juliet Tizzard (HFEA)
Cheryl Fitzgerald (St Marys)
Debbie Falconer (MFS)
Clare Brown, Infertility Network UK

A1.2 Role

- To contribute scientific and clinical expertise and real-life experience to the project.
- To approve the study protocol and any substantial amendments
- To monitor the project progress
- To advise the Steering Group on the conduct of the project