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| tuoslogo_key_cmyk_hi **The Mesothelioma and Radical Surgery Trial 2 (MARS 2)** **CONSENT*****Summary report from the MARS 2 Patient experience sub-study*** **Peter Allmark****Angela Tod****Clare Warnock****Karen Lord** |

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**Key Messages**

* The Mesothelioma and Radical Surgery Trial 2 (MARS 2) is a feasibility randomised controlled trial (RCT) recruiting and randomising participants to surgery ([extended] pleurectomy decortication) versus no surgery. All participants receive chemotherapy.
* A Patient Experience Sub-study (PESS) was conducted to generate a more in-depth understanding of the patient experience including trial interventions, participation, and consent.
* This paper reports on an initial ethical analysis of PESS data about the issue of informed consent.
* This report is based on interviews with 15 Mars 2 participants who consented to participate in the qualitative sub-study. Seven had received surgery and chemotherapy, 7 received chemotherapy and one declined randomisation.
* Twenty four interviews were conducted by telephone, including 9 follow-up interviews at 2-3 weeks post-surgery (n=6) or at 6 months post randomisation (N=3).
* A model of informed consent was used for analysis that comprises five components or criteria: capacity, information, understanding, voluntariness and consent (or refusal).

**Capacity**

* At the time of consent to MARS 2, participants had all recently received a serious life-threatening diagnosis. Diagnosis was usually at the end of a period of concern and uncertainty. The diagnosis and treatment was distressing and affected mood.

* However, none of the interview participants reported being overwhelmed by the decision to participate in the MARS 2 trial and accepting randomisation or felt incapable of making it. The interviews analysed here did not suggest a problem in relation to MARS2.

**Understanding and information**

* Some of the participants received good information about MARS 2 and were able to recount accurate information about the trial. Information sheets and the use of pictures of the scans were reported to aid understanding.
* Problems in understanding did emerge from some interviews, particularly in relation to randomisation. Example include participants thinking the computer made a judgement that a person was suitable for surgery or chemotherapy. Other participants assumed the doctor was making the decision about treatment allocation. At least one participant seemed unaware that their treatment was part of a trial.
* Trust emerged as a significant factor in some participants’ decisions to take part or stay in the trial.
* There was a huge variation within the sample in terms of their reaction to randomisation. Some considered it was in ‘the hands of the gods’. Others described being disappointed not to be randomised to receive surgery. In contrast some were relieved that they had been randomised to no surgery. The one participant who withdrew from the study after randomisation did so because of a preference for chemotherapy.
* Some participants indicated they had not understood what to expect later on in the trial. Two surgery recipients had not expected the drains, and associated problems; and one expressed disappointment that follow-up contact had not been as great as expected. One participant had sought help for psychological issues following the diagnosis and study participation.

**Voluntariness**

* In UK law a decision is taken to be not voluntary where it is made under undue pressure. Undue pressure in randomised trials relates to the concept of desperate volunteers. These are people who volunteer to take part in a randomised trial because it gives them their only chance of getting what they really want and what they would choose if they could.
* Whilst some participants did want to “*go for everything that people offer you”,* there was no indication that the notion of ‘desperate volunteer’ applied in MARS2. This was partly because there was not a good understanding of randomisation across the sample.
* A few participants reported that a clinician had expressed a preference for surgery or chemotherapy.

**Implications**

* There were few problems identified relating to capacity.
* There were issues relating to information and understanding, particularly concerning randomisation, and voluntariness; this reflects findings in other research in this area of consent.
* In the literature participants’ failure to understand randomisation is usually put down to the notion being a complex one. Alternatively, it may be that the notion is not particularly difficult in itself but that it is difficult for the patient, given their worldview, to accept that this is how their doctors are making a decision. Where participants do understand randomisation they have often described it as unfair, as indeed did one of the participants in these qualitative interviews.
* Patient preference designs are a potential solution but may not be appropriate for MARS 2 because they have implications for sample size. There is an indication from the findings that there was not an overwhelming preference for surgery. Indeed, the trial screening log indicates the most common reason for declining entry to MARS 2 is a preference for no surgery.
* An agreed response strategy to the “What would you do?” question, may help recruiters within a trial.
* These findings indicate there is room to improve ways to explain trial participation and randomisation. There is potential to learn from those clinicians who are expert practitioners and use supporting technology and visual aids.

**The Mesothelioma and Radical Surgery Trial 2 (MARS 2) Patient experience sub-study (PESS)**

**CONSENT**

***Introduction***

The Mesothelioma and Radical Surgery Trial 2 (MARS 2) is a feasibility randomised controlled trial (RCT) recruiting and randomising participants to surgery ([extended] pleurectomy decortication) versus no surgery. All participants receive chemotherapy. The intervention being evaluated in MARS 2 is a radical surgical procedure, which has huge potential implications for the patient's quality of life. In addition the participant journey through the trial is not straightforward, as consent is in two stages (participation, then later randomisation). A Patient Experience Sub-study (PESS) was therefore conducted to generate a more in-depth understanding of the patient experience of:

1. trial participation including recruitment and randomisation and
2. trial interventions (chemotherapy and surgery) and associated care and support needs.

This paper reports on an initial ethical analysis of a sub-sample of the patient qualitative data generated in the MARS 2 patient experience sub-study (PESS). It sets out what the findings revealed about the issue of informed consent. Other ethical issues emerged during the wider analysis and these will be presented and discussed in the final report of the PESS.

This paper focuses on consent and begins with the model of informed consent used for the study and data analysis. This is followed by a brief summary of the findings, presented using the components of the model as headings

***Model of informed consent***

According to a model widely used in both legal and ethical arenas, the importance of informed consent lies in an ethical principle described as, for example, respect for autonomy or self-rule [1–3]. The guiding thought is that it is ethically important for people to govern their lives in particular areas, such as what happens to their data and to their bodies. Often the word “consent” suffices; usually we talk of consent to sex rather than informed consent, for example. Consent needs to be ‘informed’ when people are making decisions that are important in terms of their autonomy but which are also complicated in some way, requiring expert guidance. Whether or not to take part in complicated medical trials is such a decision.

The act or process of informed consent to clinical studies or treatment is said to occur when someone who has capacity voluntarily consents to a study or treatment having received and understood sufficient information about it [3]. This can be restated in terms of up to five components or criteria: capacity, information, understanding, voluntariness and consent (or refusal). The point about refusal is that someone who turns down treatment or research because, say, they have misconceptions about it is just as much a problem ethically, although not legally, as one who consents with misconceptions.

This model can be used both as an ideal and as a marker of what is “good enough”; in the latter case this might mean, for example, that it is legally satisfactory; in the former, it would mean the consent was perfect and could not be improved upon. For the purposes of the qualitative study reported here we assumed that consent would be good enough, and did not analyse the interviews with a view to checking the four criteria in legal terms, for example, whether consent was given under “undue pressure”. MARS 2 has, however, a number of features that have been shown in previous studies to raise difficulties for the consent process [4–12]. These include, that the trial:

* Coincides with bad news
* Concerns treatment for a potentially lethal condition
* Concerns treatment options that are highly invasive
* Concerns treatment options that are immensely different

**Aim**

The aim of this part of the qualitative study was to see whether and, if so, where issues and problems arose that could render consent less than ideal; this was with a view to discussing possible improvements in the process for the next stage of the study.

**Methods**

Qualitative one to one, semi-structured interviews and thematic analysis.

**Setting**

The interview participants were recruited through two treatment centres (Sheffield or Leicester).

**Sample**

This report is based on interviews with 15 Mars 2 participants who consented to participate in the qualitative sub-study. Seven had received surgery and chemotherapy, 7 received chemotherapy and one declined randomisation.

The findings are based on analysis of 24 interviews (including 9 follow-up interviews). This does not include all the interviews from the PESS as all the follow-up interviews will not be completed until October 2017. The analysis is based on those interviews completed by January 2017 so that findings could be fed back in a timely manner when the MARS 2 feasibility study extends to full trial.

**Data collection**

The interviews took place at different points in the trial process. Fifteen (57%) of the 24 interviews analysed took place just after randomisation. Six (21%) were follow-up interviews with participants who received surgery, conducted 2-3 weeks after surgery. Three of the interviews were at six months post randomisation, (2 had received chemotherapy and 1 had surgery).

Participants were interviewed by telephone. Following consent, interviews were audio recorded and transcribed for analysis. All identifying data were removed from the transcripts.

***Method of analysis***

Thematic analysis was used. Quirkos is a software package for the storage, management and analysis of qualitative data and was used to support this section of the analysis. The thematic analysis itself was framed around the model of informed consent presented above; for example, the interviews were read with a view to detecting whether and, if so, what problems there appeared to be with participants’ understanding of the trial.

The Treatment Centre was not considered of great import in the analysis of informed consent in the trial. The treatment type was of interest, particularly in relation to people’s preferences before randomisation, their reaction to it, and how they felt about it later. The longitudinal element in the interviews was also considered of interest particularly in relation to participants’ view in hindsight; it may, for example, help decide what information new participants require.

A caveat is required. The data for this report is entirely derived from interviews with participants at varying points in this MARS trial and, as such, is based on participants’ memory. This has been shown to be flawed in other studies looking at consent in difficult trials [13]; for example, patients who were known to have been told about taking part in a trial reported that they had not [14]. The findings here must be read with this in view; we are looking at their memory of the experience with a view to improvements, not with a view to making judgements about any individual case of consent.

**Findings**

The report of the findings is now set out around the five components, using capacity, information and understanding, and voluntariness as subheadings. The boundaries between the components are fuzzy; for example, where someone fails to understand information given this may be linked to capacity. As such, the fact that the findings were reported under one heading rather than another is not of concern.

**Capacity**

Capacity, sometimes termed “competence”, has two aspects; it is the ability of someone (the agent) to do something (the task). In assessing capacity, therefore, both the agent and the task must be considered. In this case, the task was weighing up and deciding whether to take part in the MARS 2 study. Problems with capacity may relate to the task, the agent or a combination. None of the participants in this study were unconscious and we should assume that they were as able to undertake tasks as the general population prior to MARS 2. However, at the time of consent they had all received a serious life-threatening diagnosis.

*R1 [participant]...she did the...she came back up to me with the results and that and told me I'd got this mesothelioma and she told me it was terminal and it is inoperable. This is what she told me.*

*I: Okay.*

*R1: She told me that a few times didn't she?*

*R2: [partner] Yes. [S4]*

One participant said they had sought help for the psychological impact:

*Yes, and as well as the other business I asked our GP for…they’ve got a thing round here called Link to go and see a…like a psychiatrist and, you know, like you can talk to them. So I've booked…I've had two appointments with them because I was getting some really shitty thoughts. [S7]*

Furthermore, the diagnosis was usually at the end of a period of concern and uncertainty; some participants had had difficulty getting past gatekeepers, others had received false reassurance.

*Then he said to give me some antibiotics to try and clear it up – it was only seven days antibiotics. Anyway, then after the end of the antibiotics I went back again and she has give me another note and she said no, wait for six weeks and then go back for another x-ray...*

*I had the x-ray and as I said to the lady have you done the x-ray? She said well yes, come in and have a look - I had said to her then, I said is there any nasty illness in there? No, she said it's just loads of gunge. [S13]*

Two participants noted that the treatment, steroids and chemotherapy, affected mood but did not imply this affected their ability to make decisions.

*R1 [participant]: She certainly knew, when I was on the treatment. I see it did changed me…it wasn’t my temper…*

*R2 [partner]: No, just sharp with me, you know, which…[name of patient] as he just says, is always just so laid back [S5]*

While some participants noted these types of issue none said they were overwhelmed by the decision to participate in the MARS 2 trial and to accept randomisation or felt incapable of making it.

Capacity is rarely raised as an issue in relation to consent to trials. There are some exceptions, for example in neonatal trials where mothers have just had traumatic births [7,15,16]. The interviews analysed here did not suggest a problem in relation to MARS2.

**Understanding and information**

Proper analytical separation of information and understanding would require the collection of data from the information-giving end, ideally the observation of the points at which various professionals gave information about the MARS 2 trial to the participants. In this qualitative study this was not done. As such we only have the participant reports of the information they received which is, in truth, almost equivalent to their understanding. This one-step distance from actual information giving is hugely significant; much evidence from social psychology shows the unreliability of witness reports, and this includes evidence specific to informed consent in randomised trials. It follows that where we report the information which participants say they received this needs to be read cautiously. It is also the reason that information and understanding are reported in the same section here.

Some of the participants said they had received good information and were able to recount accurate information about the trial; one or two mentioned the information sheet as helpful. A number of participants made unprompted comments concerning how their understanding was aided through the use of pictures of the scans.

*R: Well, no, he was using images on his computer. I mean, he even had the images of my chest there off my chest drain and the scans that were done; he had copies of them, yes.*

*I: Did it help to actually visualise your own…?*

*R: Well, it did, it was absolutely brilliant I thought. [S9]*

At least one participant seemed unaware that their treatment was part of a trial. The following quote is indicative but ambiguous; the point becomes clearer in context however.

*I: Has anyone said to you in words – I mean you may not have heard them, so I'm just kind of like trying to find out what different people know about their treatment and everything. Did anyone say anything about it being randomised or have you heard that word at all?*

*R: No, well he didn't say that, he said at that time, he said I've got nine people on my programme and, you know, more or less I would be, if I went on the programme I would be the tenth. [S13]*

There was evidence of some problems in understanding, particularly in relation to randomisation. There are several examples of patients who seem to view the process as non-random. In some cases participants described the computer as receiving information about the person, which it processed and then made a judgement that, say, this person is suitable for surgery and that one for chemotherapy.

*They had a discussion with surgeons, oncologists and the team as to how the treatment had already gone on the chemotherapy and apparently it had gone well and therefore I was presumably put into the computer and it churned out, yes, I was suitable for surgery. [S15]*

*I don’t know, presumably there’s a criteria that it has to meet and obviously, because I had responded to the treatment and that’s why I got picked for the surgery. [S17]*

*R: I thought they put all the information into a computer and the computer selects you, am I wrong?*

*I: There’s not a right or wrong, it’s very much your understanding.*

*R: Yeah, no, that was our understanding of it. That they put all the results of the two, what happens on the chemotherapy side of it and they got all the results from that and put it into a computer and then the computer spits out a name. [S17]*

There were one or two cases where it seemed that the doctor was assumed to be making the decision about treatment allocation, where phrases were used relating to the doctors’ knowing best and using their judgement.

*What I said to the doctor, if you want to operate I am not frightened of surgery. If you want to do chemotherapy, go down that way. Use your judgment, do what's best in my case. [S23]*

*[The clinician] who suggested the MARS2 trial and I said to him, I said well I've got faith in you doc if you've got faith in me [S4]*

A related point, one partly illustrated in the previous quotes, is that trust emerged as a significant factor in some participants’ decisions to take part or stay in the trial.

*Yeah. Yeah, it was just complete confidence in the doctors and the surgeons. Yeah, no…well, personally, you know, I wasn't frightened of the surgery at all. You're almost kind of looking forward to it, you know, to get better. It's that sort of attitude, yeah. [S3]*

The philosopher Onora O’Neill discusses the issue of trust in relation to autonomy using informed consent as an example. She takes the view that acting on trust does not undermine autonomy and that, for example, it is acceptable for patients to ask their clinicians “what would you do?” [17–20]

Arguably, however, this is more problematic when people are research participants rather than patients; and there are some who believe that once the clinician is acting as a researcher the relationship to the participant/patient changes to the extent that trust is no longer adequate justification for the decision-making of the participant. We have criticised this view elsewhere [21] but nonetheless it remains an ethical question which those taking consent in the MARS 2 trial may need to face: if a potential trial participant asks you to make such a judgement should you be able to advice that, say, if it were a relative of yours you would advise them to take part?

In general participants seem to be motivated to take part and remain in the trial by the belief that it was best for them, although some mentioned the hope it would do good for others.

*Well, two things really. I mean, here I had this beginning of a disease which I thought would suit me best to participate and then maybe give me a better chance. And secondly I was keen to participate from a point of view of maybe people in the future. [S9]*

**Voluntariness**

In UK law a decision is taken to be not voluntary where it is made under undue pressure, as when someone is threatened to hand over their wallet [2,22]. What renders this undue is that someone is able to control good or bad consequences for the decision maker and does so in order to force a decision. Hence a GP who tells a patient that unless they do something then their condition will kill them in short order (as one participant reported here) is simply stating relevant facts for the decision-making, albeit rather bluntly; he or she is not applying undue pressure.

Legal examples of such undue pressures are usually of an extreme order and not relevant here. However the literature reports the problem in randomised trials of desperate volunteers [21,23–25]. These are people who volunteer to take part in a randomised trial because it gives them their only chance of getting what they really want and what they would choose if they could.

*The fact that I was diagnosed with this disease and that is what you do when you have been given a diagnosis like this, then you go for everything that people offer you. [S8]*

*Well when you were talking to me, when originally (local doctor) said to me, I said to him well what is the outcome? He said more or less he practically told me I've only got 12 months if I left it the way it was. [S13]*

In order to reach the point of being a desperate volunteer, however, you would need a good understanding of randomisation in the first place. As we have seen, this was not always the case for the participants interviewed in this study. One describes the 50/50 chance of getting what is wanted as okay, another as “not very fair”. Whether others would have shared this view had they understood randomisation is a moot point.

**Longitudinal issues**

Most of the interviews analysed (n=15, 57%) took place in the period immediately after randomisation; however, the remainder took place at later points: those who received surgery were interviewed two to three weeks after that; both groups were interviewed after six months; and one further interview at one year is planned. Of interest in these interviews is whether there are issues that arose over time that are not clear or present in the initial interviews.

The first of these issues was actually clear in some of the earlier interviews, although it sometimes became more obvious later. This was the reaction to randomisation. There is no obvious pattern here as the following quotes show:

*I: At that point did you have any preferences?*

*R: No, because not knowing either of how the chemotherapy would affect me or what the computer would decide. It was sort of all in the hands of the gods really. [S8]*

*I: How did you feel when you heard you were going to be having further chemotherapy?*

*R: I felt quite positive because I was considering that the surgical option was much more serious and much more involved. [S18]*

There were a few more respondents who were disappointed not to be randomised to receive surgery or who were relieved that they had been.

*I was a bit disappointed that I hadn't been picked obviously for the operation because I thought well...that's being a bit selfish sort of thing, you know. That was the whole idea of the trial. Some going down one path and some going down the other. The most disappointing thing was the wife was getting a bit uptight because we hadn't heard from anybody. [S21]*

The one participant who had withdrawn from the study after randomisation had a preference for chemotherapy, making their decision to withdraw seem fairly rational from their point of view:

*I: Was it the surgery in particular that you were worried about?*

*R: I think so. [S32]*

As well as their own views, participants occasionally reported that the clinician had also expressed a preference:

*if it was part of my family, he said, I'd go down the surgery route. So that was, like, we just said okay. [S30]*

*if surgery was available as well as chemotherapy he would probably go down that, you know, if he had the ability to affect the outcome he would hope for it and probably would want it and equally if it was his family ... However, he did again reinforce the point that there is no evidence. He said that you could be entering into…and [thoracic surgeon] said this, you could be entering into unnecessary treatment which is radical in nature, will require a huge amount of recuperation time and recovery et cetera et cetera. [S22]*

And the following quote, given at length, illustrates a number of points, including disappointment, difficulty in understanding, and, perhaps, how people come to terms with this.

*Well they told us everybody who comes onto the MARS2 trial will get two lots of chemo to start with and [X] said after that, well they both said after that, they said it's a decision not made by us, you know, it's made by computer sort of thing. They said because we don't pick and choose because obviously we would want all the good...you know and he says it will be a case then of either being picked to have the operation or if you go down the other road, it's just chemo. We accepted that. But when you get thinking at home, you know, you're thinking about it and I thought to myself it would be nice if I did have the operation because I was prepared to go through with it even if I didn't come out of it because I am a philosophical chap and I always think if it doesn't help me, it will help somebody else further on down the line, you know. But you know hardly a day goes by without you thinking of what's going to be. I was thinking of having the operation, if I successfully got through it...I didn't know when or how often or what they give me after that. I know they were going to give more chemo after the operation but how soon after I don't know. We didn't go into it that deep because obviously we hadn't been picked by then. [S4]*

The follow-up interviews of those who had received surgery did not suggest that many participants had been surprised by any particular points: two of them had not expected the drains; one was pleasantly surprised that they had not suffered much pain: and one expressed disappointment that the interest in them during follow-up had not been as great as expected. There was only one follow-up interview with someone following chemotherapy; this did not raise new issues, although it was a participant [S7] who had sought help for psychological issues following the diagnosis and study.

**Implications**

Using the framework set out earlier, the interviews appear to show that there were few problems relating to capacity, but there were issues relating to information and understanding, particularly concerning randomisation, and voluntariness; this reflects findings in other research in this area of consent.

The problem of participants’ failure to understand randomisation is widely reported in the literature. This is usually put down to the notion being a complex one. Alternatively, it may be that the notion is not particularly difficult in itself but that it is difficult for the patient, given their worldview, to accept that this is how their doctors are making a decision [26]. Where participants do understand randomisation they have often described it as unfair, as indeed did one of the participants in these qualitative interviews. It may also be the case that clinicians feel uneasy with the use of randomisation and hence describe it in ambiguous ways.

There are alternative research designs that might overcome this problem: patient preference designs are one possibility. There is some indication from the findings here that there would not necessarily be an overwhelming preference for surgery. Indeed, the trial screening log indicates the most common reason for declining entry to MARS 2 is a preference for no surgery.

Another alternative is pre-randomised consent (or Zelen) randomisation. A modified version of this has recently been developed in which a cohort is set up and consent to have their data used in studies, that cohort is randomised, but only those who receive the trial treatment are asked to consent further [27,28]. There are implications for statistical power in such a design; if any in the treatment group decline participation then there is a large knock-on effect for sample size; this could be an important problem for trials where potential participant numbers are small.

Within the existing design, clinicians might consider how they approach the “what would you do” question. It may help to agree a response strategy for recruiters at the beginning of a trial. Our own view is that it would be acceptable to say you would advise a family member to take part in a study but avoid any appearance of preference towards one arm or the other.

As a practical tip, it seems that the use of visual aids, particularly the scan pictures, was liked by patients. It might be that a visual representation of randomisation, such as those used in protocols, might also be helpful for participants. These finding indicate the room to improve ways to explain trial participation and randomisation. There is potential to learn from those clinicians who are expert practitioners and use supporting technology and visual aids.

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