Unblinding following trial participation: qualitative study of participants' perspectives.

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Abstract

Background: The implications of offering unblinding to trial participants to treatment arm after trial completion have been little explored.

Purpose: We sought to explore trial participants' perspectives on whether they would like to be unblinded as to the treatment arm to which they were allocated following involvement in a large RCT.

Methods: We conducted semi-structured interviews with 38 women who had participated in a trial during suspected pre-term labour, and had received the results of a long term follow up study that identified adverse outcomes for children in some of the treatment groups. Participants were sampled purposively. Analysis was based on the constant comparative method.

Results: Most women reported that they wanted to know the treatment arm to which they had been allocated. While the primary motive for some was curiosity, many others wanted to know as part of an attempt to understand or explain their child's current health problems. These women were motivated by a search for a coherent causal narrative, even though unblinding was unlikely to be able to meet their aspirations. Some participants identified potential disadvantages in discovering their treatment allocation, including feeling responsible for their child's health status, and some women were very clear that they did not want to know their treatment group.

Limitations: A purposive sample was used and the extent to which it represents the views of all participants in the study is not established.

Conclusions: Important challenges arise in offering to unblind trial participants, whatever the trial results. Participants may need help and support to understand the limitations of the knowledge they gain through being unblinded and to decide whether they wish to know to which treatment arm they were allocated.

Keywords: clinical trials, unblinding, results, participants, feedback, qualitative

Introduction

The methodological reasons for blinding trial participants to their treatment allocation are well established. Failure to blind people to treatment assignment can influence both response to the treatment and what is reported about the treatment, as well as potentially influencing professionals' management of the patient [1]. If no follow-up studies are planned, these considerations are no longer relevant once the trial is completed. Alongside the increasing pressure to provide feedback on study findings to participants [2], there is growing support for offering trial participants the opportunity to be unblinded after the end of a trial [3]. Available evidence, however, suggests that participants may have a less than 50% chance of being informed of treatment allocation to placebo after trial completion [4].

The limited evidence to date suggests that trial participants generally want to be unblinded to treatment allocation on trial completion, and that few patients report concerns at finding out to which trial arm they were allocated [3,5]. But in trials where analysis reveals adverse outcomes for some participant groups, the possible unblinding of participants may be less straightforward. The ORACLE Children's Study (OCS) is an example of such a study. The OCS [6,7] was a long-term follow up of children who had been born to participants in the ORACLE trial, an RCT investigating two broad spectrum antibiotics for women at risk of pre-term birth [8,9]. The OCS found an increased risk of long term adverse outcomes for children in some of the intervention groups, including a higher risk of cerebral palsy (see Boxes 1 & 2).

[INSERT BOXES 1 & 2 HERE]

OCS participants who had opted to receive feedback were provided with a written summary, in leaflet form, of the results of the study [10]. The leaflet presented the results separately for the two conditions for which women were being treated in the trial – preterm rupture of the membranes (PROM) or spontaneous preterm labour (SPL). The study findings varied depending on the presenting condition. A covering letter reminded each woman which *condition* she presented with

when she joined the ORACLE trial, and directed her to the most relevant set of results within the leaflet. Women were not advised in the covering letter of the *treatment arm* to which they had been allocated. The trial team decided not to make an explicit offer to participants of an option of unblinding as to their treatment, in part because of practical constraints, but more importantly because such an offer would involve unknown risks, including the potential to cause distress or other harmful effects for some participants. The leaflet offered details of a study-run helpline that participants could call if they wanted to discuss the results further. If a woman rang the helpline and expressed a wish to know to which treatment arm she had been allocated, an offer of unblinding was made.

A detailed report of work to develop, deliver and evaluate a consultative approach to inform the provision of aggregate feedback about these research findings to participants has been previously published [10]. In this paper, we focus explicitly on participants' perspectives on unblinding following their receipt of the leaflet reporting the OCS findings. In doing so, we draw on sociological work on illness narratives. Broadly speaking, illness narratives refer to the story-telling and accounting practices that occur in the face of illness [11]. While narratives about illness can be understood in several different ways, and serve a variety of functions [12,13], one important way of understanding an illness narrative is as a device through which individuals can create and give meaning to their social reality [14]. Illness narratives can be used by people as a resource in explaining disease causation, including an account of why an illness is affecting either them or someone close to them [12,13]. Constructing an illness narrative about why something has happened can help in overcoming ambiguity and uncertainty [15,16]. The telling and re-telling of a story can help people to deal with an altered situation and the associated disruption through helping to restore some sense of order [17]. In light of the increased risk of adverse outcomes for children in some of the ORACLE trial's intervention groups, we draw on the illness narrative concept to explore and explain women's preferences for unblinding.

Methods

We conducted semi-structured interviews with 38 women who had participated in the original ORACLE trial, and whose children had been followed up in the OCS. The West Midlands Research Ethics Committee gave approval for this interview study.

Recruitment

Of the 11050 women who participated in the original ORACLE trial, 6494 were followed up in the OCS. Of these, 4676 requested that they received the findings of the OCS. These women were sent a leaflet reporting the OCS aggregate results, as well as a questionnaire to assess their responses [10]. The questionnaire was returned by 1124 women, 382 of whom agreed to be contacted for an interview. Women who lived within a hundred mile radius of Leicester (a city in the East Midlands of the UK) (132) formed the sampling frame for this qualitative study. We used purposive sampling to ensure that we would access a diverse range of views and experiences. Sampling was based on participants' self-reported level of understanding of the results leaflet; their emotional reactions to the leaflet (as reported in the questionnaire); and whether their child was affected by any of the conditions mentioned in the feedback leaflet (a functional impairment, cerebral palsy, and/or a bowel problem). Of the 47 women we invited to take part in an interview, 9 declined or dropped out.

Interviews

Semi-structured interviews were carried out by CJ, who was independent of the OCS team. The interviews were conducted using an interview prompt guide based on a review of the literature and discussions within the project team. The guide was used to help structure the interviews, but was used flexibly in response to the ways in which participants wanted to take the interview. Interviews focused on the impact of receiving a summary of the findings of the OCS and participants' understandings of, and views about, the feedback they had received, with a specific focus on issues of unblinding. Each interview lasted for approximately one hour and was digitally audio-recorded.

Consistent with the approach used by the OCS study team, the interviewer did not explicitly make an offer of unblinding, but did ensure that women were aware that this was possible if they expressed a desire to be unblinded during the interview.

Analysis

All recordings were transcribed verbatim and anonymized. Data analysis was based on the constant comparative method [18]. Constructs from the literature on illness narratives served as sensitising concepts [19] and were used to guide, but not constrain, the coding. Initially, each transcript was read carefully and preliminary codes used to describe each unit of meaning. After this, an iterative process of comparison across the transcripts (including identification and exploration of deviant cases) was used to develop a coding framework that grouped the preliminary codes into organising categories or themes. Throughout this process categories were carefully checked and modified where necessary, in order to ensure a robust fit between the data and the codes. The final coding frame was programmed into NVivo software and was used to process the data systematically.

Findings

Details of the sample

Thirty-eight women were interviewed. Participants were aged between 28 and 59 years (average age 39). The majority (23) were working in a variety of occupations across the socioeconomic spectrum. Those who were not currently in paid employment were predominantly at home with family responsibilities, with a few unable to work due to sickness or disability. There was little racial diversity in the sample; all but three participants were of 'white British' or 'white Irish' ethnicity. The age at which they left education varied from 15 to 23 years, with 8 women having a degree level qualification.

At the time their ORACLE child was born, women reported being between 24-41 weeks pregnant (average 34 weeks), with almost two thirds (25) reporting premature rupture of the membranes. The

length of time between recruitment to the ORACLE clinical trial and giving birth was reported as between a few hours and 17 weeks. Participants had between one and five children. For half of participants, the ORACLE child was their first baby.

At the time of interview, the children born to women who took part in the ORACLE trial ranged from 8-13 years old (average 10 years). A minority (6) of participants in our qualitative study reported their ORACLE child had no health problems. The remaining 32 women reported their children had a range of health problems of varying severity including: cerebral palsy (5 children); other neurological problems (6); learning difficulties (8); bowel problems (3); respiratory problems, mainly asthma (6); psychological or emotional difficulties, predominantly behavioural problems (9); physical functioning problems (5); and visual problems (5).

Reasons for wanting to be unblinded: the search for narrative completion

Most women (24/38) explicitly indicated during interviews that they would like to know their individual treatment allocation. This desire was motivated by a range of reasons. For some participants (6), it was framed in terms of general curiosity.

It would be intriguing to know which bit of the study I'd been in, whether I'd actually had the drugs or whether I'd had placebo or whatever, it'd be quite interesting to know (Participant 12)

I think it's just curiosity really. I wanted to know whether I was on the antibiotic or the placebo one, that's all I wanted to know. (Participant 20)

There did not appear to be anything at stake for these women – they were not seeking the information for any particular purpose above and beyond 'closing the chapter' on their participation within the ORACLE Trial and the subsequent OCS. Many women, however, had more clearly

formulated reasons for wanting to find out their treatment allocation. The most common (11 participants) was to try to make sense of, or explain, their child's current health problem(s), and in particular, to identify whether these problems were attributable to their participation in the ORACLE trial.

One of the main reasons that I would have liked to have known as well what I'd had, whether it'd been a placebo or not, was my little boy, he suffers with a digestive tract problem
(Participant 18)

...part of me wanted to know the findings because I wanted to make sure that me taking a medication hadn't...wouldn't cause him any long-term...any long-term problems. (Participant 10)

These women had important and potentially very sensitive questions that they thought knowing their treatment allocation could help them answer. They knew they had taken part in the ORACLE trial, and that their child had health or functioning problems, but they wanted to know whether there was a causal link: they wanted to locate their experiences within a narrative of cause and effect.

Illness narratives, in the way we use the concept in this paper, are constructed by people as a way of explaining and understanding the occurrence of illness. This almost inevitably includes the question "why me?" or, in this case, "why my child?" – a question which these women believed being unblinded to their treatment allocation would help them answer. Unlike other attempts to create meaning, such as placing events in particular categories, the construction of an illness narrative explicitly seeks to place the illness episode within a wider social context and make links to other events as a way of generating a causal explanation [14]. This process (sometimes referred to as

‘emplotment’) involves the generation of hypotheses that may link particular episodes together. Understood in this way, women’s desire to know their treatment allocation could be seen as an effort at narrative completion – to get a better idea if the trial was a likely cause of their child’s health problems, or to gain reassurance that it was not. They described feeling as though a piece of their story was missing, and thus experienced a form of narrative frustration.

Knowing the unknowable

Women tended to assume that finding out to which treatment arm they had been allocated would give them a definitive answer as to whether participating in the trial had caused their child’s health problems or not, and therefore help them complete a narrative of causality. They framed finding out their treatment allocation as a valid and reliable way of testing a personal hypothesis that their trial participation was a causal link in their child’s health problem.

I wanted to know if anything that had happened was directly because of any medication that I might have taken, at that time when he was about to be born (Participant 03)

This was a very unlikely outcome of allocation disclosure, since the results of the trial provided indications only of increased risk, not of direct causal effects for any individual (although knowing they had been allocated to placebo may have brought some reassurance). For example, a woman who had a child with cerebral palsy, who discovered that she had received the implicated antibiotic, might conclude that her trial participation caused her child’s condition. However, the cerebral palsy could have developed even if she had been allocated to the placebo group: children who are born pre-term are at higher risk of cerebral palsy. In addition, as the use of antibiotics for women in pre-term labour had started to become a feature of clinical practice in some maternity units at the time of the ORACLE trial, she might have received them even if she had not participated. Women who wanted to be unblinded to test the hypothesis “it was my trial participation that caused my child’s

problems” wanted to ‘know the unknowable’, and it is not clear to what extent the women interviewed in this study recognised this. The following is the only example in our dataset of a participant demonstrating this recognition.

Whether I’d had a placebo or what had I had, it doesn’t tell me clearly whether, what or why my son has cerebral palsy, do you know what I mean? (Participant 29)

Negative consequences of unblinding: the potential costs of narrative completion

Although many women wanted to find what they regarded as the missing part of their narrative, some did recognise that finding out about their treatment allocation could be a double-edged sword and that there may be costs associated with completing their narrative. Most obviously, women feared they could end up feeling responsible for adverse outcomes if they found a possible causal link between their actions (taking part in the trial), and their child’s health problems. Some women felt strongly that the potential costs needed to be carefully balanced against the potential benefits.

I think that if your child just happens to have had some problem with their bowel and then you find out which medication you were given [...] it’s very difficult isn’t it, if you’re kind of left with that that actually you taking part in a trial may well have caused your child’s problems. I don’t think it’s a very comfortable place to be. (Participant 10)

Many women in the trial had experienced pre-term birth, which in itself is associated with a high risk of adverse outcomes for children. Women who had lost a baby, or had a child with disabilities, had often already constructed narratives with which they were comfortable, and which had allowed them to come to terms with their experience. Discovering their treatment allocation had the potential to disrupt this narrative, and some women wanted to avoid this. Three participants were sure they did not want to know to which arm of the trial they had been allocated. These women

wanted to avoid counterfactual thinking [20] – reflecting on the ‘what ifs’ – and to avoid feeling guilt and self-blame.

I don't know if their analysis can go back to the individual and they can tell you which combination, 'cos the statistics were related to having the two antibiotics combined. And you'd have to go back to know whether you were on the two antibiotics combined, and I don't know if that could be tracked back for an individual patient, I suspect it should be able to, and I'm assuming therefore I could track back, but I've not chosen to. I can't change anything [...] it was my decision. (Participant 08, child with cerebral palsy)

The possibility of discovering they had been allocated to one of the intervention arms, and hence could have exposed their child to the risk of harm, was not the only unwelcome scenario participants discussed. Some women believed that being in the trial had helped their baby, and wanted to protect this belief. For one woman the possibility of finding out that she might have been in the control group, and therefore not received antibiotics which she believed could have saved one of her twins, was of great concern, even though her belief was not well-founded.

I want to know that I did everything I could do to improve the chances of my babies surviving [...] I wouldn't want to know anything that I may have done, like taking part in a study like this, I wouldn't want it pointed out to me that if I hadn't have took part in the study my babies might have had more chance of surviving [...] Well it's a possibility, if I was in the placebo group and the fact that, well it says here [the antibiotics were] helpful to babies in the short-term after they've been born. (Participant 05)

Therefore, while many women believed that individualised results could complete the story for them (and recognised there could be some negative as well as positive consequences), others had already

constructed a narrative with which they were comfortable, and wanted to avoid disrupting it through gaining any further information that could cast doubt on the causal links they had made between events.

Discussion

We explored trial participants' perspectives on the potential of being unblinded after they had received a summary of the results of a trial in pregnancy which found risks of harm associated with the antibiotics administered in the trial. Our findings suggest that knowing the trial outcomes in aggregate, but not knowing their own treatment allocation, could result in a sense of narrative frustration for participants who wanted to better understand the reasons for their children's health problems. Their participation in the ORACLE trial often appeared to them to be a possible candidate for providing an explanation – particularly as women had received information indicating that the follow-up Oracle Children's Study found an increased risk of long term adverse outcomes for children of mothers who had received antibiotics in the trial. Their urge for narrative completion was understandable given evidence of the difficulties individuals experience in coping with medical uncertainties or ambiguities, particularly in relation to aetiology [21]. However, because of the limitations of scientific method, the information about treatment allocation that the women sought was unlikely to provide the certainty or narrative resolution they desired. Thus, there are some indications that participants' reasons for wanting to be unblinded were based on false assumptions about the potential for unblinding to reveal previously obscured causal relationships and thus enable completion of the narrative arc.

Our study also suggests some caution about the extent to which a desire for unblinding is universal among trial participants. Some participants recognised that revelation of their treatment group could potentially bring risks as well as benefits, and that one of those risks was disruption of an existing narrative. A potentially complex decision-making process therefore had to be undertaken

that weighed up the potential benefits of knowing (perhaps being able to complete the story) against the potential costs (feeling responsible for their child's outcomes). Some women actively wished to avoid finding out their trial allocation in order to avoid disrupting their established narratives about their child's health and progress, and to avoid guilt and self-blame. Again, any causal link between trial participation and individual outcomes would be uncertain, but the risk of these emotional reactions was real.

In contrast to other studies of participants' views of unblinding [3,5], our interviews were not linked to an explicit offer to unblind participants as to their treatment allocation. As a result, the women in this study were not discussing their actual experiences of being unblinded (or choosing not to be), but rather the possibility of finding out their treatment allocation more generally. While a limitation in some ways, this does perhaps mean that women could talk more freely without any pressure to account for a decision about whether or not to be unblinded. A further possible limitation is that our sample is not representative of all ORACLE trial and OCS participants, though it did, through its use of purposive sampling [22], ensure inclusion of participants with a diverse range of views and experiences. Socio-cultural characteristics of the interview sample were broadly representative of the OCS. Given that our study was conducted in the context of pregnancy, where clinical trials have remained rare and the population under study raises distinctive ethical and other issues [23], the generalizability of our findings to other areas is unclear. Trials undertaken during pregnancy may be especially emotionally fraught as the costs of participation (if adverse outcomes are shown for any groups) may be borne by someone other than the trial participant i.e. the unborn child. However, our work does suggest some important areas for consideration and future research.

Our work suggests that people may need help and support to decide whether or not they wish to know to which treatment arm they were allocated. This may be especially important in a trial that reveals unexpected or unwelcome findings in some treatment groups, but may also apply to other scenarios, including one where one treatment arm does much better than others. It is relatively common for new treatments to perform less well than standard treatment in trials: around 20% of

published Phase III trials in adult oncology show significantly better outcomes for the control than the intervention group [24], and evidence suggests that new treatments for childhood cancer tested in Phase III trials are equally likely to be inferior as to be superior to standard treatment [25]. This is to be expected given the principle of equipoise, but it also opens up possibilities for regret and self-blame for people in the group deemed to have poorer outcomes if they are unblinded to treatment allocation.

If an offer to unblind participants is planned following the conclusion of a trial then care needs to be taken to ensure that this process is handled sensitively, and that appropriate support to make such a decision, and cope with the consequences, is offered. An especially important element of this is the need to take all possible steps to ensure that participants understand what they know after having been unblinded and how far this information allows them to validly test their hypothesis and complete their narrative. It may be especially important to stress what they can justifiably extrapolate from knowing their treatment allocation, and what is still uncertain and ultimately unknowable.

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BOX 1: The ORACLE trial

The ORACLE trial evaluated the effects of prescribing erythromycin or co-amoxiclav for women with either preterm rupture of the membranes (PROM) or spontaneous preterm labour (SPL) with intact membranes and no overt infection, using a 2x2 factorial design.

Findings

For women with PROM

- Erythromycin was associated with prolongation of pregnancy and improvements in short-term maternal and neonatal morbidity; for singletons there was a reduction in the composite primary outcome (death or abnormal cerebral ultrasound or use of supplemental oxygen at 36 weeks post menstrual age).
- Co-amoxiclav was associated with increased risk of neonatal necrotising enterocolitis.

For women with SPL

- There was no evidence of either benefit or harm at discharge from hospital.

BOX 2: The follow-up ORACLE Children Study (OCS)

The ORACLE Children Study (OCS) sought follow up information for surviving children at 7 years of age in the UK using a parent-report postal questionnaire. Primary outcome was defined as the presence of any level of functional impairment using the Multi-Attribute Health Status (MAHS) classification system. Secondary outcomes included a range of medical and behavioural outcomes. Educational attainment at 7 years was assessed for children resident in England using results from National Curriculum tests at Key Stage 1.

Findings

For children whose mothers had PROM

- Prescription of antibiotics seemed to have little effect on the health and educational attainment of children at 7 years.

For children whose mothers had SPL

- Prescription of erythromycin was associated with an increase in the proportions of children with any level of functional impairment from 38 to 42%.
- Increase in the proportions of children with cerebral palsy from 1.7 to 3.3% associated with erythromycin and from 1.9 to 3.2% with co-amoxiclav.
- There was a suggestion that more children who developed cerebral palsy had been born to mothers who had received both antibiotics.