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Factors influencing the participation of older people in clinical trials – data analysis from the MAVIS trial

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ABSTRACT

Background

Older people are less likely to be included in clinical trials. Little is known about factors influencing older people's decisions about participating in clinical trials.

Objectives

To examine the views of older people about participating in clinical trials.

Methods

Postal questionnaire to 801 participants who had completed the MAVIS nutrition trial, aged 65yrs and older. Closed and open questions sought participants' views about factors important to them when deciding to take part in a trial, features of the MAVIS trial they liked and disliked and changes they would suggest.

Results

540 (59% of MAVIS trial participants) returned the questionnaire. The most important reasons reported for taking part in the trial were helping the research team and medical knowledge, and helping other older people. Participants valued good communication with the trial staff and good organisation. Participants reported concerns about swallowing pills and taking a placebo. Participants reported that future participation in trials could be influenced by poor health status.

Limitations

This questionnaire surveyed older participants who had taken part in a randomised controlled trial. It did not elicit the views of people who had withdrawn or never decided to take part in the trial.

Conclusions

Older people report altruistic reasons for taking part in trials. Simple trial designs, which minimise demands on participants and maintain good communications should be preferred. Explaining the need for older people, despite poor health, to participate in trials may help the generalisability of clinical trials.

Key words: randomised controlled trial, patient participation, older people, nutrition

Running heading: including older people in trials

Trial Registration Number: ISRCTN 66376460

BACKGROUND

The randomised controlled trial (RCT) is widely accepted as the most powerful method to evaluate the effectiveness of new health technologies. However, low accrual and retention of participants can restrict the value of the trial, reducing the statistical power and generalisability [1,2]. A recent review reported that 31% of trials funded by the UK Medical Research Council and National Health Service Research and Development Health Technology Assessment Programme that recruited participants between 1994 and 2002 did not achieve their original recruitment target [3]. Older people, in particular, are less likely to be included in RCTs, restricting generalisability further [4].

Studies which have examined factors influencing trial recruitment have often focussed on cancer trials [1,2,5,6] or hypothetical trials [7]. Trial recruitment is influenced by clinician and patient factors. Clinician barriers identified [1,2,5] include time pressures and constraints, lack of staff and training, concern about the impact on the clinician-patient relationship, concern for the patients, loss of professional autonomy, and lack of reward and recognition. Barriers to participant accrual and factors influencing participation in RCTs include the extra demands of the study (e.g. additional procedures and appointments), patient treatment preferences and treatment uncertainty [1,2,5]. Factors affecting older people's views on taking part in RCTs have seldom been examined.

The aim of this study was to explore the factors that influence older people to take part and remain in randomised trials through surveying participants who had completed a randomised controlled trial investigating the effect of multimineral and

multivitamin supplements on infections, known as the Mineral And Vitamin Intervention Study (MAVIS trial) [8].

METHODS

The MAVIS trial design

The MAVIS trial was a randomised, double blinded placebo-controlled trial which investigated the effect of a multimineral and multivitamin supplement on infections, health service use and quality of life in 910 community-dwelling people aged 65yrs and older in the Grampian region of Scotland. Full details of the trial are provided elsewhere [8]. Grampian Research Ethics Committee gave approval for the study. All older people covered by the general practices involved were eligible to take part, unless their general practitioners (GPs) had indicated that they were too unwell to be contacted, or they already took vitamin or mineral supplements. Eligible older people were recruited by mailing them an initial invitation from their GP. Those who indicated they were interested returned a reply by post and were invited to an appointment in the GP's surgery.

Participants were asked to take one tablet a day for one year. They were also asked to record daily in a diary whether they had an infection and any contact with primary care for infection. At the end of each month participants returned the diary by post to the trial office, together with a questionnaire about trial tablet consumption over the last seven days. Ten percent of participants were also randomly selected to take part in a tablet count at six months and one year, requiring them to return unused tablets at these time points. Questionnaires for the Euroqol (EQ-5D) [9] and Short-Form-12 (SF-12) [10] were completed at the GP visit and sent out at six months and one year.

Participants also completed digit span forwards [11] and verbal fluency [12] cognitive function tests at recruitment, and then by phone at one year. Two researchers were involved in recruitment (a research nurse and a research dietitian). Both researchers conducted the subsequent cognitive function tests by phone. Participants were also phoned shortly after recruitment to check that there were no concerns about the study. The two researchers or trial secretary also phoned participants if diaries or questionnaires were not returned after one postal reminder, or if there were queries about information provided in the diaries.

After the end of the trial all participants who had not withdrawn or indicated they wished no follow-up were given details of their trial allocation and the results of the trial by post (801 of the 910 randomised). They were then sent this reply-paid follow-up questionnaire by post, which contained closed and open questions about taking part in RCTs. No postal reminders were sent out for this questionnaire.

Follow-up questionnaire

The questions asked were informed by the findings from Prescott and colleague's systematic review [1,2] and consultation with Professor Vikki Entwistle from the University of Dundee. Closed questions asked about motivating factors for taking part in a trial, health professional involvement, randomisation, use of a placebo, and filling in questionnaires. Quantitative methods were used to analyse participants' responses to closed questions in the questionnaire. Categorical data were analysed using Chi-squared tests. Two-sided statistical significance was at the 5% level. For dichotomous variables odds ratios (ORs) are presented with 95% confidence intervals (CIs) for the proportion of participants responding to the closed questions

that were asked (active treatment vs blinded placebo). When comparing response rates for the proportions answering the closed questions between the treatment groups, non-responders were not included in the analysis. Participant data were stored, manipulated and analysed using SPSS version 11.5.1.

The open questions focused on participants' experience of the trial specifically asking *"Would you consider taking part in a research study again, if asked?"* We also looked at aspects that they liked by asking: *"Are there things that you liked about the study?"* *A*spects that respondents disliked were also of interest, respondents were asked: *"Are there things that you disliked about the study?"* Respondents' recommendations on how to improve the trial were also sought by asking: *"Is there anything that you would have changed about the study?"*

Content analysis, a systematic method for assigning text to content categories [13] was used by PF to analyse the data given in response to open questions from the questionnaire. Responses from all open questions were read and reread, and the categories were generated through close inspection and comparison of the data. A second researcher (SM) assisted with analysing a sample of responses for each question to enhance the reliability and reproducibility of the coding. The coded data set was then entered into an Access database. The themes of the analysis are illustrated using representative quotations.

RESULTS

Five hundred and forty (59%) of all 910 MAVIS trial participants returned the questionnaire. Participants responding to the questionnaire did not differ by gender, type of residence or smoking status from all those randomised to the trial. However, they averaged one year younger than those recruited to the trial (data not shown). There was no statistically significant difference in proportions responding to the questionnaire between different arms of the trial [OR 1.12; 95% CI (0.83, 1.51); p = 0.450] see Table 1.

Closed questions

There were no statistically significant differences in response rates to the closed questions between active and placebo arms of the trial, see Table 2. Overall, 86% of those responding to the survey reported that helping the research team was very important to them when deciding to take part in a study like MAVIS. Seventy-two percent of people rated helping other people like themselves as being an important issue when deciding to take part in a study like MAVIS.

Under half of the people reported that being asked to take part by a doctor was very important to them. Whereas being asked by a nurse was rated to be less important when deciding to take part in a study. Thirty-four percent of respondents from the active treatment arm and 40% from the placebo arm reported that reducing their risk of illness was important to them when deciding to take part in a study.

Less important issues were knowing what was in the tablets, filling in a questionnaire or a diary. Least important issues were having to take tablets and having treatment decided by chance, particularly the possibility of having to take a placebo.

Open Questions

Written responses to the open questions are grouped into positive and negative aspects of the MAVIS trial, and factors impacting on people's considerations about taking part in future research.

Positive aspects of trial participation

Trial communication and organisation

Good communication and friendly personal contact between participants and trial staff seemed particularly important to people in the trial (n=88):

> *"I liked the friendly approach of those members of the team with which I came into contact with".* [Participant 011100.]
>
> *"I liked the regular communication between researchers and subject. This gave me a good feeling about the quality of the study."* [Participant 011012.]
>
> *"You kept in touch and I felt part of the programme."* [Participant 011021.]
>
> *"Over the period in question, I was treated with kindness and helped throughout."* [Participant 022009.]

Participants indicated that they liked the way in which the trial was organised and conducted by trial staff. In particular MAVIS trial participants made specific

reference to the value of face-to-face interviews, the design of the diaries, receiving Christmas cards and the general "friendliness" of those involved in the trial (n=52):

> *"The instructions were clearly understood. The face-to-face interview with a member of the research team was excellent. The layout of the diaries and the colour coding of the pages was also very good and easy to complete."* [Participant 011095.]
>
> *"It was very well organised."* [Participant 052038.]
>
> *"I thought it was very well organised. The research nurses were very friendly and it was specially kind of them to send out cards to us at Christmas."* [Participant 032025.]

Participants also reported that they had liked the simplicity and "straightforward" nature of their involvement (n=76):

> *"So easy and filling up the diary was no problem."* [Participant 011060.]
>
> *"Very simple and straightforward, no complication."* [Participant 011130.]
>
> *"It was very simple to take part."* [Participant 021008.]

Infection Diaries and questionnaires

Although some people reported positive feelings towards completing their infection diary and completing questionnaires, this was the most frequently reported negative aspect of the trial (n=21). Some respondents suggested that instead of a daily diary they would have preferred a weekly diary:

> *"I am not too keen on questionnaires but I know how important they are to research."* [Participant 091025.]
>
> *"Having to make a day-to-day diary and filling in forms and such like."* [Participant 011145.]
>
> *"All the writing (which is done by my wife!)."* [Participant 022055.]
>
> *"I would have favored a weekly diary rather than a daily one."* [Participant 21048.]

Uncertainty of placebo and taking pills

A number of people reported having concerns related to taking pills. Participants reported disliking having to swallow the pills as they found this difficult, or struggled to remember to take them each day (n=16):

> *"I would have excluded the placebo."* [Participant 091069.]
>
> *"I would rather have known what type of tablet I was taking."* [Participant 011090.]
>
> *"Not knowing if I was taking a vitamin or a dummy."* [Participant 011038.]
>
> *"Wondering if it was placebo."* [Participant 011087.]
>
> *"No - although a bit wary not knowing whether the tablet was a 'smarty' or the real thing."* [Participant 012057.]
>
> *"Being already on a lot of pills, my dislike was having to take more."* [Participant 012052.]
>
> *"I'm not very good at swallowing capsules or tablets."* [Participant 022025.]
>
> *"Having to remember to take the tablet each day."* [Participant 041057.]

Some MAVIS participants reported having issues with the possibility of receiving a placebo, as they didn't know what treatment they had been allocated to (n=12). A small number of people indicated that they would have preferred to receive the active treatment as opposed to the placebo. Only one participant from the active arm reported that they would have liked to know what the pill actually contained:

> *"I would prefer to see what results would be if I had taken minerals and vitamins."* [Participant 091040.]
>
> *"I would have preferred a share of the vitamin tablets as during the last 6 months, I thought the tablets contained vitamins so I was fooled."* [Participant 032010.]
>
> *"Not really. But it would have been interesting to know what the real tablets consisted of, especially as I was informed that I had been on the real tablets and not the placebos."* [Participant 092028.]

Duration of the trial

On the whole MAVIS participants were positive about the one year duration of the trial. However, a small number of participants stated a dislike about the duration and commitment required of them during their participation of the trial (n=6). It was suggested that a study for a six-month period would have been preferable and more convenient to them. In terms of feedback of the trial results, a small number of participants (n=6) indicating that they would like to have known the trial outcome sooner. However, the length of time taken to conduct the trial may have been greater that expected by the participants due to the staggered recruitment:

> *"The length of time the survey carried on for and the commitment necessary to see it through."* [Participant 011090.]
>
> *"Having wasted a year taking the placebo, I would have preferred if it had been 6 months vitamins and minerals and 6 months placebo, but still a blind test."* [Participant 31015.]
>
> *"Perhaps the length of your study. A six-month study might have been better. Most volunteers went on holiday during the year and you feel having to take tablets while you were away was an inconvenience. In my case I was in Australia."* [Participant 92077.]
>
> *"Perhaps knowing the outcome a bit sooner - after a year you are inclined to forget if the vitamins made any difference to your health."* [Participant 042059.]

Taking part in future research

It became clear, that when participants were asked if they would consider taking part in future research, their responses reflected their experiences of being a participant in the MAVIS trial. Participants reported both reasons for and against taking part in future research. In total, over half of the 540 MAVIS respondents indicated that they would be willing to take part in future research (n=283).

Altruism

The most commonly described motivation by respondents for taking part in future research seemed to be based on a desire to "help" (n=181). Respondents described wanting to help other patients (n=92), and helping contribute towards furthering medical knowledge (n=76). The notion and desire to help by participating was a recurring theme throughout the data:

> *"Yes, if it was going to help others."* [Participant 011129.]
>
> *"Yes, because I like to think such research studies make meaningful contributions to medical knowledge and science."* [Participant 011012.]
>
> *"Yes, if the research will help elderly people in the future, then the study is worthwhile."* [Participant 011006.]

Giving something back

It was reported that participants' decisions to take part in the MAVIS trial and trials in general included the consideration of being able to "giving something back" to the health service by taking part in the trial (n=18):

> *"Yes. NHS has served me well over the years. Taking part in studies is my way of saying thank you."* [Participant 11018.]
>
> *"Yes, to put something back into the health service."* [Participant 11107.]
>
> *"Yes, if the studies appear to be worthwhile. A long time ago I did some research in a very different field and liked to be associated with research again even if the connection was very minor."* [Participant 011045.]

Weighing up future participation in trials

Some people's willingness to take part in future research appeared to depend on their expected involvement in the specific study, and any perceptions of personal benefit that might be gained through their participation:

> *"I might consider taking part, depending on what the research was. The reason is that it would probably help others in the future."* [Participant 011081.]
>
> *"Yes, but only if I felt comfortable about it and that would depend on what I had to do for the study."*
>
> [Participant 011002.]

Of the 540 respondents around a fifth reported their unwillingness to participate in future studies (n=117). Additionally some participants' considered how "worthwhile" a study would be when considering taking part in future research (n=15). The most frequently reported reason for not wishing to take part in future research was related to participants' perceptions of age and poor health status which were perceived as potential barriers towards taking part in any future study (n=32):

> *"Due to my age, I would not consider it practical for me to take part in any future research studies."* [Participant 011147.]
>
> *"I think not. There is a reluctance to take on commitments, which may not be completed or become an increasing burden at my time of life. Resources of energy become increasingly depleted."* [Participant 011089.]
>
> *"Just now I am having hospital tests. So until I am finished I couldn't consider at the moment to take part in any study."* [Participant 011028.]
>
> *"No. I feel I have done my share. This year I discovered I had CLL, which is being treated with tablets. I have also had a hernia operation recently."* [Participant 022012.]

Personal interest in study and results

Some participants reported their involvement in the trial as being "interesting" to them (n=17). Receiving feedback from the trial regarding the study's findings was an aspect of the trial that some people reported liking (n=16). A number of participants also reported that trial participation gave them a "routine" which fitted into their lifestyle (n=15):

> "*Yes. I found it very friendly and most interesting.*" [Participant 041084.]
>
> "*I liked being kept in the picture of what was happening and the results.*" [Participant 022096.]
>
> "*It was easy to take part and did not interfere with my normal routine.*" [Participant 011062.]
>
> "*Taking tablet medication was a simple and easy thing to do, and there was no weighing of food included, so it was a simple routine to keep to.*" [Participant 011024.]

DISCUSSION

There are many barriers that prevent older people from taking part in randomised trials, restricting the value of trial findings.

Designing trials with older people

We found that the notion of "helping" is an important motivating factor in older people's decisions about participation in RCTs. Ways in which participants reported helping included helping other patients and helping by contributing to medical knowledge. Other studies have found similarly altruistic reasons for people to take part in research [1,2,5,7,14-16]. Although, it is not clear whether older people demonstrate more altruism than younger people.

Participants reported that their participation would "depend" on the demands of the trial, which will vary depending on the design of individual trials. Others have also identified that people's decisions to participate depend on additional demands such as taking trial medication or additional travel and appointments [5,15]. It would be advisable to keep demands on participants to a minimum and make the trial as simple as possible, including providing transportation or covering its costs [17]. Some participants of the MAVIS trial referred to keeping the daily infection diaries and pills as being "easy" and "straightforward". In particular, it is important to remember that this age group may already be taking several daily multiple dose medications in addition to any trial medication.

Regular communication and the friendly approach used by the trial team was an aspect of the trial that participants valued, as was good organisation and the way in which the trial was conducted. Given the age and state of health of some participants communication may be particularly important as they may live alone and have limited contact with other people. Similar social reasons for older people to take part in trials have also been found by Schron *et al* [18].

A small number of MAVIS participants felt that they would have preferred to receive the results sooner. As recruitment was staggered it took longer for those recruited at the start of the trial to receive feedback on the results than those recruited at the end of the trial. It would be advisable to discuss the duration of the trial and the time taken to receive feedback of the results to people at recruitment.

Some participants had concerns regarding the placebo, which have been reported in other studies [1,2,5,15,19,20]. It is particularly important to have adequate time to clearly explain the reasons for randomisation and a placebo, concepts which are difficult for participants of all ages to grasp and recall [5-7,16,21].

Planning trials with older people involves considerations specifically for this age group, and potential participants should be involved in the study design process [7]. Some people felt that their health and age would not allow them to take part in a trial or that they might not be of use to the trial as they were too old. Ill health and depression in this age group are particularly important reasons for discontinuing a trial once enrolled [22]. Explaining the need for older people, despite poor health, to participate in trials may help the generalisability of clinical trials. Trial staff need to

be sensitive to these issues, as well as avoiding prejudicial terms such as 'geriatric', which may discourage older people from participating [23].

Limitations

The results of this study must be interpreted within the context of the MAVIS trial – participants completed the questions having already taken part in the trial and had received the trial results. We did not seek responses from people refusing to participate in the trial which would have given a broader perspective.

The questionnaire was not piloted with older people prior to administration, as it was not feasible due to the very short timescale of the funding. However, the questions asked were provided by researchers who had already undertaken research on patient participation in trials. Piloting the questionnaire may have identified potential issues which could have been addressed [24].

The questions were asked in the order of closed questions first, followed by open questions. The closed questions may have prompted participants' responses to the open questions that followed. However, using both closed and open questions in that order is useful for topics about which little is known [25].

Analysis of data from open questions was primarily conducted by one researcher, which may potentially introduce researcher bias. To help reduce such biases a second researcher (SM) independently checked a sample of responses for each question.

The nature of the trial and those involved may have affected the results and generalisability of the findings. The trial investigated the effect of multimineral and multivitamin supplementation on infections (particularly common infections like upper respiratory tract infections), which may be viewed as less severe conditions than cancer or heart disease. The multimineral and multivitamin supplement may have caused less concern about possible side-effects - an important issue for older people [21,23,26]. Thus participants' responses may be less relevant to participants recruited to trials related to life-threatening illnesses. Most MAVIS trial participants were under 85yrs of age, so findings may not be generalisable to the oldest old.

Conclusions

Older people have often been excluded from clinical trials as a direct consequence of exclusion criteria focussing on pre-existing illnesses and medication use, rather than age *per se* [6]. With the need to ensure that older people are represented in clinical trials, we need to ensure that concerns of older people are properly addressed.

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Table 1: Flow chart of MAVIS trial participants

	Active treatment arm N (%)	Placebo arm N (%)
Total N randomised	456	454
N sent questionnaire	402 (88)	399 (88)
N responding to questionnaire	266 (58)	274 (60)*
Age - mean [SD]	72 [5]	72 [5]
Aged ≥85	5 (2)	8 (3)
Sex female	132 (50)	125 (46)
Sex male	134 (50)	149 (54)
Current smoker	32 (12)	26 (10)
Lives in the community	259 (97)	271 (99)
Lives in a nursing home	7 (3)	3 (1)

* OR 1.12; 95% CI (0.83, 1.51); p = 0.450

Table 2: Which of these are important to you when deciding to take part in a study like MAVIS?

	Active treatment arm N=266			Placebo arm N=274			p-value
	Not at all n (%)	A little n (%)	A lot n (%)	Not at all n (%)	A little n (%)	A lot n (%)	
a. The research will help other people like me	6 (2)	56 (21)	191 (72)	7 (2)	62 (23)	197 (72)	0.928
b. The research will help the research team	3 (1)	27 (10)	227 (85)	1 (1)	30 (11)	236 (86)	0.565
c. Taking part may reduce my risk of illness	38 (14)	121 (45)	89 (34)	52 (19)	102 (37)	109 (40)	0.068
d. Being asked by a doctor to take part	61 (23)	70 (26)	112 (42)	67 (25)	77 (28)	117 (43)	0.960
e. Knowing what is in the tablets	112 (42)	69 (26)	71 (26)	115 (42)	75 (27)	70 (26)	0.918
f. Having the possibility of taking a dummy tablet (a placebo tablet)	164 (62)	63 (24)	24 (9)	159 (58)	65 (24)	36 (13)	0.309
g. Being asked by a nurse to take part	83 (31)	88 (33)	73 (28)	85 (31)	94 (34)	79 (29)	0.967
h. Having to take tablets	130 (49)	66 (25)	54 (20)	141 (52)	67 (24)	57 (21)	0.952
I. Having my treatment decided by chance	114 (43)	82 (31)	52 (19)	115 (42)	81 (30)	62 (23)	0.708
j. Having to fill in questionnaires or diaries	109 (41)	75 (28)	66 (25)	114 (42)	83 (30)	66 (24)	0.91

Percentages may not calculate to 100% as not all people completed the questions.