

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form ([see an example](#)) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Parental comprehension of the benefits/risks of first line randomized clinical trials in children with solid tumors
AUTHORS	Chappuy, H�el�ene; Bouazza, Naim; Minard-Colin, Veronique; Patte, Catherine; Brugi�eres, Laurence; Landman-Parker, Judith; Auvrignon, Anne; Davous, Dominique; Pacquement, H�el�ene; Orbach, Daniel; Tr�eluyer, Jean Marc; Doz, Fran�ois

VERSION 1 - REVIEW

REVIEWER	Valerie Shilling Research Fellow University of Exeter Medical School UK no competing interests
REVIEW RETURNED	06-Mar-2013

REPORTING & ETHICS	I do not think this research is required to conform to specific reporting guidelines (please correct me if I am wrong) however the reporting conforms broadly with STROBE. Please could the authors provide further details on study recruitment rates? how many families were approached to take part in the research and particularly, how many approached had consented to and declined the main trial? What was the recruitment rate overall to main trials? Only 4 families were interviewed that had declined the main trial. I assume this reflects a recruitment bias but without the main trial recruitment information it is not clear. Given that the understandings and misunderstandings of families that decline a trial may well be different to those of families that consent, I think the bias and the potential impact on the findings of the study need to be addressed.
GENERAL COMMENTS	41: These arguments are also put forward in article ref 24 – the authors might like to reference this article in association with this paragraph as well. Minor points: Page 11 line 45 is ‘willing’ the correct word? Typographic error p12 line 45 ‘fulfill’ Figure 1 please label the charts M1 and M6 and change the scale of the y axis or include actu

REVIEWER	Wim Pinxten Senior Research Fellow Erasmus University Medical Center Rotterdam The Netherlands
REVIEW RETURNED	12-Mar-2013

<p>THE STUDY</p>	<p>I am not a native speaker English, but I think the language could be improved if a native speaker checked the text.</p> <p>The abstract should be rewritten: the background is actually the objective etc. It is sometimes difficult to interpret when not reading the article itself: for example 'Results: forty first interviews...' - you can only know what is meant with 'first interviews' when reading the paper.</p> <p>Abstract and key messages: -parents tend to underestimate the risks - as written in the summary, recalling and underestimating are used as synonyms. Please clarify. -the understanding of some components of informed consent may be equivalent to recall. This is very suggestive, and needs further clarification.</p> <p>Introduction: -In the second paragraph, a number of problems with regard to informed consent are raised (lack of direct benefit, information). Other problems also exist. Please clarify against the background of literature or the legal requirements for informed consent why these issues selected, and others are neglected. -'however, the patients participating in a trial might not benefit directly themselves; instead, the outcome of the studies provides information about future treatment options': Please reconsider the formulation of this statement: it sound very unusual to state that patients do (not) benefit themselves in clinical research - the benefit is rather a characteristic of the trial than of the participation in it. It also concerns 'potential' future treatment options.</p> <p>Sample population: -Have ALL parents been asked to consent (except for those who consented in another language than French)? If not, for what reason/based on what criteria? -'retranscribed'? - transcribed?</p> <p>Instrument -I am not a methodologist, but I seriously doubt whether it is possible to identify elements predictive of a good understanding of the information at the time at which consent is sought in a (heterogeneous) sample of this size. Nonetheless, exploratory findings could be relevant to set up further research on the topic. -I am not the right persons to judge upon the appropriateness of the tests that are used to compare quantitative data.</p>
<p>RESULTS & CONCLUSIONS</p>	<p>some of the elements of the research protocol were well understood, but not by all the parents. So how can they decide? Although not yet demonstrated in pediatrics to our knowledge, quality of life is a crucial element in the decision of parents'.</p> <p>-here, the problem stated is the understanding of some of the parents, while the approach is about motivation. Parents may have strong motivations but still poor understanding...</p> <p>-I do not think that it is properly demonstrated that quality of life is a crucial element, so it would be more correct to change 'is' in 'could be', or to add a reference.</p>
<p>GENERAL COMMENTS</p>	<p>Nice paper, enjoyed reading it.</p>

VERSION 1 – AUTHOR RESPONSE

Reviewer: Valerie Shilling

I do not think this research is required to conform to specific reporting guidelines (please correct me if I am wrong) however the reporting conforms broadly with STROBE.

Please could the authors provide further details on study recruitment rates? how many families were approached to take part in the research and particularly, how many approached had consented to and declined the main trial? What was the recruitment rate overall to main trials? Only 4 families were interviewed that had declined the main trial. I assume this reflects a recruitment bias but without the main trial recruitment information it is not clear. Given that the understandings and misunderstandings of families that decline a trial may well be different to those of families that consent, I think the bias and the potential impact on the findings of the study need to be addressed.

The sentence has been added in the manuscript: "During our study period, 53 families were approached to participate in a randomized clinical trial. Forty families have been interviewed in our study. Our recruitment rate was 75%. Thirteen families were non interviewed for several reasons: the delay of one month was exceeded or the physicians have forgotten to propose our study."

Our rate is very strong and limits the bias suggested by the reviewer.

This is a most interesting article which adds to the quite substantial body of literature on understanding in informed consent. I have just a few further points to ask the authors to address.

Article summary

Article focus – the author guidelines for this section state that it should contain bullet points on the research questions or hypotheses. The points in this section do not have this specific focus.

This part has been modified.

Strengths and limitations: I find point two unclear. I think the authors are suggesting that because there is a one month lag between recruitment and interview, parents responses in interview reflect their true understanding rather than rote recall – but could they please clarify?

The sentence has been modified: "The parents were asked to participate in this study closely to having consented. Thus, the risk of recall bias was limited."

Methods

Why have the questions used to assess comprehension been reported but not the questions used to explore decision making? This would greatly help the reading of the results section on 'reasons for participation and physician's influence on the decision to participate'.

The four questions concerning the decision making are detailed in the method section: "How difficult was it to take the decision you took concerning the participation of your child in this protocol?", "What were the principal elements underlying your decision?", "Who do you feel took the final decision?" and "What do you expect from the doctor?".

Results

Could the authors explore in greater detail the responses of parents who declined the main trial? The paragraph starting page 9 line 27 suggests that parents who declined were less likely to see direct benefit of the trial for their child. This would seem to be an important observation yet little is made of this here or in the discussion. Was this the only observed difference in the responses of families that declined the trial? I realise that limited conclusions can be drawn from the responses of only 4 families however as this group is notoriously hard to recruit it seems a shame not to explore their responses more.

Effectively, in the manuscript, we have made the choice not to discuss this point as only four parents that declined the main trial.

It seems that the understanding of the benefits was lower in this population: none was able to describe specifically the potential benefits. This ratio (0/4) has been included in the manuscript.

The table describe the responses of 4 parents who declined the trial:

complete partial none
research participation 2 1 1
aim 1 1 2
protocol 1 3 0
randomization 2 1 1
individual benefit 0 0 4
collective benefit 1 3 0
risks 0 2 2
alternative 4 0 0
voluntary participation 4 0 0
duration of participation 1 3 0
freedom to withdraw 4 0 0

Discussion

The authors suggest some interesting reasons for why parents might have poor recall of the specific risks of the trials (p12 lines 1-19) are the authors able to link these explanations to previous evidence?

The reference number 27 has been added.

Page 12 paragraph beginning line 41: These arguments are also put forward in article ref 24 – the authors might like to reference this article in association with this paragraph as well.

The following sentence has been added in the manuscript: “As suggested by V. Shilling, [28]”

Minor points:

Page 11 line 45 is ‘willing’ the correct word?

The sentence has been modified in line with the reviewer’s comment.

Figure 1 please label the charts M1 and M6 and change the scale of the y axis or include actual % inside the bar so that it is possible to tell from the chart more clearly/accurately the %

The Figure 1 has been modified accordingly.

Reviewer: Wim Pinxten

I am not a native speaker English, but I think the language could be improved if a native speaker checked the text.

The manuscript has been extensively revised by a professional scientific editor.

The abstract should be rewritten: the background is actually the objective etc. It is sometimes difficult to interpret when not reading the article itself: for example 'Results: forty first interviews...' - you can only know what is meant with 'first interviews' when reading the paper.

The following sentence has been added in the background: “Patients and their parents must necessarily receive appropriate information to allow them to make truly autonomous decisions about participation in randomized clinical trials (RCTs). Few data are available that reflect the full spectrum of pediatric oncology clinical research.”

Abstract and key messages:

-parents tend to underestimate the risks - as written in the summary, recalling and underestimating are used as synonyms. Please clarify.

We have modified the sentence in the abstract.

-the understanding of some components of informed consent may be equivalent to recall. This is very suggestive, and needs further clarification.

The sentence has been modified: "The parents were asked to participate in this study closely to having consented. Thus, the risk of recall bias was limited."

Introduction:

-In the second paragraph, a number of problems with regard to informed consent are raised (lack of direct benefit, information). Other problems also exist. Please clarify against the background of literature or the legal requirements for informed consent why these issues selected, and others are neglected.

The text has been modified to be clearer.

-'however, the patients participating in a trial might not benefit directly themselves; instead, the outcome of the studies provides information about future treatment options': Please reconsider the formulation of this statement: it sound very unusual to state that patients do (not) benefit themselves in clinical research - the benefit is rather a characteristic of the trial than of the participation in it. It also concerns 'potential' future treatment options.

This sentence has been deleted.

Sample population:

-Have ALL parents been asked to consent (except for those who consented in another language than French)? If not, for what reason/based on what criteria?

The sentence has been added in the manuscript: "During our study period, 53 families were approached to participate in a randomized clinical trial. Forty families have been interviewed in our study. Our recruitment rate was 75%. Thirteen families were non interviewed for several reasons: the delay of one month was exceeded or the physicians have forgotten to propose our study."

-'retranscribed'? - transcribed?

The word has been modified as suggested by the reviewer.

Instrument

-I am not a methodologist, but I seriously doubt whether it is possible to identify elements predictive of a good understanding of the information at the time at which consent is sought in a (heterogeneous) sample of this size. Nonetheless, exploratory findings could be relevant to set up further research on the topic.

-I am not the right persons to judge upon the appropriateness of the tests that are used to compare quantitative data.

The statistical analysis was made by a professional methodologist of our clinical research unit. The number of patients was taken into account in this analysis.

(Minor comments)

'As shown above, some of the elements of the research protocol were well understood, but not by all the parents. So how can they decide? Although not yet demonstrated in pediatrics to our knowledge, quality of life is a crucial element in the decision of parents'.

-here, the problem stated is the understanding of some of the parents, while the approach is about motivation. Parents may have strong motivations but still poor understanding...

-I do not think that it is properly demonstrated that quality of life is a crucial element, so it would be more correct to change 'is' in 'could be', or to add a reference.

The sentence has been modified as suggested by the reviewer.

Nice paper, enjoyed reading it

VERSION 2 – REVIEW

REVIEWER	Wim Pinxten ErasmusMC Rotterdam The Netherlands I have no competing interests
REVIEW RETURNED	15-Apr-2013

- The reviewer completed the checklist but made no further comments.