**Participation in a clinical trial for a child with cancer is burdensome for a minority of children**

Ivana M.M. van der Geest1, 2, MD, Marry M. van den Heuvel-Eibrink2, MD, PhD, C. Michel Zwaan1, MD, PhD, Prof. Rob Pieters2, MD, PhD, Prof. Jan Passchier3, PhD,

Anne-Sophie E. Darlington4, PhD

1 Department of Paediatric Oncology/Haematology, Erasmus MC-Sophia Children’s Hospital, Rotterdam, The Netherlands

2 Princess Maxima Centre for Paediatric Oncology, Utrecht, The Netherlands

3 Department of Clinical Psychology, VU University Amsterdam, The Netherlands

4 University of Southampton, Faculty of Health Sciences, Southampton, United Kingdom

**Corresponding author:**

DrA-S E Darlington, University of Southampton, Faculty of Health Sciences, Southampton SO17 1BJ, United Kingdom. Email: a.darlington@soton.ac.uk. Tel. +44(0)23 8059 7888

**Running Title:** Parents’ experiences of cancer trials

**ABSTRACT**

**Aim:** This study explored how parents who had lost a child to cancer felt about them taking part in a clinical trial.

**Methods:** A retrospective questionnaire was sent to parents who had lost a child to cancer. They were asked whether their child took part in a clinical trial during their palliative phase, their motives for their child’s participation, how they perceived their child’s burden and whether they would, hypothetically speaking, enrol again.

**Results:** The 24 parents of 16 deceased children who had participated in a clinical trial explained their motives for their child’s participation. The most common answers, with multiple responses, were treatment for future patients (n=16), hope for a cure (n=9) and prolonging their child’s life (n=6). Eight parents said that participating was not burdensome for their child and four said it was very burdensome, with others answering in between. None of the parents would decline participation if they would be in the same situation again.

**Conclusions:** Performing clinical trials, even in a vulnerable population, such as children with cancer at the end of life, may not always lead to increased burden. None of the parents would in future, given the same circumstances, decline participation in a clinical trial.

**Key Words:** Burden; Cancer; Children; Clinical trial; Palliative care

**KEY NOTES**

• There is a lack of evidence around parents´ perceptions of the burden that their child may experience when participating in a clinical trial.

• Participating in a clinical trial, for potentially vulnerable children with cancer at the end of life, does not always lead to increased burden.

• None of the parents would in future, given the same circumstances, opt out of having their child participate in a clinical trial.

**INTRODUCTION**

Involving children in clinical trials is essential to improve evidence-based medical care for children and test the value of novel, promising anti-cancer medication ([1](#_ENREF_1" \o "Zwaan, 2010 #39)). Knowledge obtained from pharmacological research performed in adults cannot simply be transferred to children, as children differ from adults in terms of pharmacokinetics and paediatric formulations ([1](#_ENREF_1" \o "Zwaan, 2010 #39)). A change in the regulations on drug testing has been advocated in The Netherlands ([2](#_ENREF_2" \o ",  #112)) and the aim of this broader regulation is to increase the inclusion of children in studies investigating the effect of new, promising anti-cancer drugs ([2](#_ENREF_2" \o ",  #112)). Numerous organisations have encouraged this change in legislation, such as Innovative Therapies for Children with Cancer, a European academic consortium for drug development for treatment of childhood cancer ([1](#_ENREF_1" \o "Zwaan, 2010 #39)).

The participation of children with incurable cancer in a clinical trial is an ethically debatable topic ([3-6](#_ENREF_3" \o "Fine, 2003 #96)). On the one hand, children are being asked to undergo a potentially harmful treatment, which for children with incurable cancer can be controversial, as they often experience many physical complaints and/or restrictions during the palliative phase ([7](#_ENREF_7" \o "Wolfe, 2000 #120)). On the other hand, children have the right to receive licenced medication, which requires investigation. In addition, some children might potentially respond to novel anti-cancer drugs ([8](#_ENREF_8" \o "Lee, 2005 #75), [9](#_ENREF_9" \o "Horstmann, 2005 #71)), which can offer both the parents and the child hope ([10](#_ENREF_10" \o "Carter, 2011 #114)).

Studies performed in the field of paediatric oncology have identified several reasons why parents let children with incurable cancer participate in clinical trials, including altruism, the need to continue treatment directed at the disease, the desire to prolong their child’s life and hope for a cure or a miracle ([11-18](#_ENREF_11" \o "Maurer, 2010 #28)). A study that explored the perspectives of clinical trial participation from the point of view of adolescents, reported that most of the adolescents hoped that participation would result in a direct benefit for themselves ([19](#_ENREF_19" \o "Miller, 2013 #115)). Ulrich et al has stated that more understanding of the parents’ rationale for participation in clinical trials was necessary ([20](#_ENREF_20" \o "Ulrich, 2004 #41)).

Scarce information is available about the child’s burden of participation in clinical trials ([21](#_ENREF_21" \o "Tomlinson, 2007 #101)). A qualitative study with six parents of children undergoing haematopoietic stem cell treatment showed that most parents were positive about taking part in clinical research ([17](#_ENREF_17" \o "Keusch, 2014 #51)). Research in healthy children and children with a chronic disease reported no significant unpleasantness from participating in medical research ([22](#_ENREF_22" \o "Hunfeld, 2012 #5)). It is important to understand whether parents felt that participation was burdensome for their child, based on systematically collected information, which may improve further care.

Therefore, the aims of the present study were to examine: whether the child with incurable cancer participated in a research study for a new treatment (clinical trial), why the parents participated, the child’s perceived burden and whether parents would, given the same circumstances, participate in a research study for a new treatment.

**PATIENTS AND METHODS**

**Participants**

The participants in this study were parents who lost a child to cancer between 2000 and 2004, during or after treatment at the Department of Paediatric Oncology/Haematology, Erasmus Medical Centre, Sophia Children’s Hospital, The Netherlands. In total, the parents of 123/135 children were eligible for this study. The parents of 12 children were not approached to participate in this study as it was thought too burdensome (n=five), because their child died in the diagnostic phase of childhood cancer (n=two) or their child died because of a sudden toxic death during treatment (n=two). In addition, the parents of two prematurely born infants were not approached, as both infants had multiple organ problems, and died very shortly after birth and one family was seeking asylum at the time of their child’s death ([23](#_ENREF_23" \o "van der Geest, 2014 #129), [24](#_ENREF_24" \o "van der Geest, 2015 #113)). A questionnaire was sent to all 246 parents, as part of a larger study in which we explored parents’ perspectives of paediatric palliative care ([23](#_ENREF_23" \o "van der Geest, 2014 #129), [24](#_ENREF_24" \o "van der Geest, 2015 #113)). The median follow-up time between the child´s death and completion of the questionnaire was five years, with a range from three to eight years. This study was approved by the Medical Ethics Committee of the Erasmus Medical Centre, Rotterdam, The Netherlands (MEC number 2007-362).

**Measurement instrument**

The questionnaire was developed based on an extensive study of the literature, clinical experience and a pilot study that included interviews with three bereaved mothers from the Dutch Childhood Cancer Parent Organisation. The current study focused on the subset of questions in Table 1. The demographic characteristics of the child were collected, including gender, age at death and diagnosis, categorised as haematological malignancy, solid tumour or brain tumour. We also documented the parents’ gender and age.

**Data analysis**

The data were analysed using Statistical Package for Social Science version 21.0 (SPSS Inc, Illinois, USA). Descriptive analyses were generated for all variables. Continuous data are presented as medians and ranges and categorical data are presented as numbers and percentages. Qualitative analyses using a framework approach were used to analyse the findings of the open-ended question, in which parents were asked why they would or would not participate again in a clinical trial in future ([25](#_ENREF_25" \o "Ritchie, 2003 #109)). Both parents were asked to complete the questionnaire. The data on one child was excluded, as the parents had not given a consistent answer to the question about participation. When one of the parents did not know whether the child had participated in a clinical trial, documentation of the child’s participation was based on the other parents’ answer to this question.

**RESULTS**

The questionnaire was completed by 89 parents of 57 deceased children, a response rate was approximately 35% ([23](#_ENREF_23" \o "van der Geest, 2014 #129)), and of these, 74 parents of 49 children completed the question about participation in a clinical trial. In total, 24 parents of 16 children (33%) opted to have their child participate in a clinical trial to test new medication, 45 parents of 31 children (63%) chose not to and five parents said that they did not know. The parent and child characteristics of those who did and did not participate in a clinical trial are depicted in Table 2.

Parents were allowed to give multiple reasons for participation and these were: treatment for future patients (n=16); hope for a cure (n=9); prolonging their child’s life (n=6) and various other reasons (n=5). Two other considerations included: the child wanted to participate and another child was cured with this medication. The remaining parents who replied other did not specify their reasons clearly.

The parents were asked “to what extent did you feel this was burdensome for your child“ on a scale of one to five, eight parents scored this a one (not burdensome), and four parents scored it a five (very burdensome). The remaining parents responded with scores between two and four (Figure 1). We also asked the parents “would you, given the same circumstances, participate again in a research study for a new treatment?”: 17/24 parents (71%) responded yes, six parents did not know, none of the parents said no and one response was missing. Of the 17 parents who would consent to their child participating again in a clinical trial, 14 outlined their reason(s) in an open-ended question. Four themes were identified that explained why they would participate again in a clinical trial: altruism, the perceived benefits for the child, having explored all possibilities and the child’s wish to participate. Some parents underscored the importance of a limited burden of participation.The themes and corresponding quotes are presented in Table 3.

**DISCUSSION**

This retrospective study explored parents’ views about their child with incurable cancer, participating in a clinical trial during the palliative phase. We focused on the perceived burden for the child during the trial and how bereaved parents viewed their experiences of participation in retrospect, including whether they would participate in another clinical trial if the circumstances were to arise again.

Approximately one-third of the children with incurable cancer in our sample participated in a clinical trial during the palliative phase. Making decisions about enrolling in clinical trials, or letting their child receive supportive care, is one of the most difficult decisions parents can face as their child nears death ([16](#_ENREF_16" \o "Hinds, 2005 #29), [26](#_ENREF_26" \o "Hinds, 2001 #60)). Some parents experience difficulties around the decision to let their child participate, because they feel that there is no other option for their child besides participating in the clinical trial ([13](#_ENREF_13" \o "Deatrick, 2002 #36)). In agreement with previous studies, our study indicated that improving care for future patients was the main driver for clinical trial participation ([12-18](#_ENREF_12" \o "Barrera, 2005 #37)). Previous studies around participation of children and/or parents at the end of life in research other than clinical trials reported similar motives ([27](#_ENREF_27" \o "Steele, 2014 #100), [28](#_ENREF_28" \o "Dyregrov, 2004 #107)). Parents may have redefined their goals and find comfort in giving meaning to their child’s life ([6](#_ENREF_6" \o "Rapoport, 2009 #99), [27](#_ENREF_27" \o "Steele, 2014 #100), [29](#_ENREF_29" \o "Hill, 2014 #104)). Several parents in the current study participated in the trial because they hoped their child might be cured, although a cure was very unlikely in these children. Parents and children who consider participation should therefore be aware of the realistic outcomes of a clinical trial ([10](#_ENREF_10" \o "Carter, 2011 #114), [30](#_ENREF_30" \o ", 2000 #134)). Other parents stressed of prolonging their child’s life. Parents’ hope for a cure and/or wish to prolong their child’s life possibly reflect the vision of being a good parent in relation to making decisions ([31](#_ENREF_31" \o "Bluebond-Langner, 2007 #55), [32](#_ENREF_32" \o "Hinds, 2009 #33)). This concept is defined as making decisions in the child’s best interest ([16](#_ENREF_16" \o "Hinds, 2005 #29), [32](#_ENREF_32" \o "Hinds, 2009 #33)). Parents recognise their role in the incurable illness trajectory as seeking further treatment options along with symptom-directed and supportive therapy ([31](#_ENREF_31" \o "Bluebond-Langner, 2007 #55)). Since we asked parents in retrospect for their reasons for participation in a clinical trial, this could bias the actual number of parents for whom these reasons were of value. It is possible that parents changed their motives over time, following changes in their hopes and goals for care as their child’s physical condition changed ([29](#_ENREF_29" \o "Hill, 2014 #104), [33](#_ENREF_33" \o "Granek, 2013 #105)).

The current study was the first that showed that participation in a clinical trial was only perceived as very burdensome for a minority of children. This finding is an important contribution to this underdeveloped field in paediatric palliative care. None of the parents would decline participation in a clinical trial if confronted with a similar decision in future. This is congruent with a qualitative study performed in children and parents of children undergoing haematopoietic stem cell transplantation ([17](#_ENREF_17" \o "Keusch, 2014 #51)). Hence, performing clinical trials, even in a vulnerable population such as children with cancer at the end of life, seems important to parents and children.

The question remains about what physicians can do to best support parents who are considering clinical trial participation for their child with incurable cancer. Adding to the current standards of providing informed consent for paediatric clinical trials, such as giving clear and detailed information about the clinical trial ([10](#_ENREF_10" \o "Carter, 2011 #114), [34](#_ENREF_34" \o "Baker, 2013 #58)), it might be helpful to explore parents’ patterns of thinking, for instance whether they are locked into thinking that their child can be cured. This is valuable as parents with different perspectives might have different care goals as a result ([11](#_ENREF_11" \o "Maurer, 2010 #28)). For instance, parents who choose supportive care alone during the palliative phase focus more often on the fact that the child will not survive and minimising the child’s suffering ([11](#_ENREF_11" \o "Maurer, 2010 #28)). Healthcare professionals might help parents to strike a balance between the benefits of participation in a clinical trial, but also preserving the child’s needs and protecting them from severe suffering ([11](#_ENREF_11" \o "Maurer, 2010 #28), [17](#_ENREF_17" \o "Keusch, 2014 #51), [27](#_ENREF_27" \o "Steele, 2014 #100)).

The strength of this study is that we demonstrated some new and important contributions, particularly the burden of participation and whether or not parents would enrol their child again, which positively add to the limited information in this field. This study has several limitations. First, we did not have any additional information on why some parents perceived their child’s participation as burdensome and whether the burden was physical or psychological in nature. In addition, it is possible that children suffered during the palliative phase, which committed parents to participation in the clinical trial. In addition, caution on the conclusions that can be drawn is important because of the limited sample size, recall bias and the retrospective design. Lastly, the use of a single unvalidated Likert scale to measure parents’ perceived burden of clinical trial participation limits the present study.

In future, there is a need to collect information prospectively before, during and after a clinical trial, in order to support our findings, to have a better understanding of the parents’ and child’s perspectives, and assure that parents have realistic expectations of what the trial might be able to achieve for their child. Understanding parents’ reasons for not enrolling in a clinical trial, and a more in-depth exploration of the nature of the child’s burden would provide valuable information.

**CONCLUSION**

The results of this retrospective study showed that one-third of children with incurable cancer in our sample participated in a clinical trial. Treatment for future patients was the most frequent rationale reported by parents who decided to enter a clinical trial, followed by hope for a cure and prolongation of the child’s life. A minority of parents reported that participation placed a burden on the child. None of the parents would, given the same circumstances, decline participation in a clinical trial. Performing clinical trials, even in a vulnerable population such as children with cancer at the end of life, may not always lead to increased burden.

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No conflicts of interest.

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**REFERENCES**

1. Zwaan CM, Kearns P, Caron H, Verschuur A, Riccardi R, Boos J, et al. The role of the 'innovative therapies for children with cancer' (ITCC) European consortium. Cancer Treat Rev. 2010; 36:328-34

2. Commissie Doek. Advies medisch-wetenschappelijk onderzoek met kinderen. 2009. Available from: <http://www.rijksoverheid.nl/documenten-en-publicaties/kamerstukken/2009/11/26/advies-commissie-doek.html>. Accessed April 16th, 2015.

3. Fine PG. Maximizing benefits and minimizing risks in palliative care research that involves patients near the end of life. J Pain Symptom Manage. 2003; 25:S53-62

4. Stevens T, Wilde D, Paz S, Ahmedzai SH, Rawson A, Wragg D. Palliative care research protocols: a special case for ethical review? Palliat Med. 2003; 17:482-90

5. Duke S, Bennett H. Review: a narrative review of the published ethical debates in palliative care research and an assessment of their adequacy to inform research governance. Palliat Med. 2010; 24:111-26

6. Rapoport A. Addressing ethical concerns regarding pediatric palliative care research. Arch Pediatr Adolesc Med. 2009; 163:688-91

7. Wolfe J, Grier HE, Klar N, Levin SB, Ellenbogen JM, Salem-Schatz S, et al. Symptoms and suffering at the end of life in children with cancer. N Engl J Med. 2000; 342:326-33

8. Lee DP, Skolnik JM, Adamson PC. Pediatric phase I trials in oncology: an analysis of study conduct efficiency. J Clin Oncol. 2005; 23:8431-41

9. Horstmann E, McCabe MS, Grochow L, Yamamoto S, Rubinstein L, Budd T, et al. Risks and benefits of phase 1 oncology trials, 1991 through 2002. N Engl J Med. 2005; 352:895-904

10. Carter BS, Levetown M, Friebert SE. Palliative Care for Infants, Children, and Adolescents: A Practical Handbook. Baltimore, MD: Johns Hopkins University Press; 2011

11. Maurer SH, Hinds PS, Spunt SL, Furman WL, Kane JR, Baker JN. Decision making by parents of children with incurable cancer who opt for enrollment on a phase I trial compared with choosing a do not resuscitate/terminal care option. J Clin Oncol. 2010; 28:3292-8

12. Barrera M, D'Agostino N, Gammon J, Spencer L, Baruchel S. Health-related quality of life and enrollment in phase 1 trials in children with incurable cancer. Palliat Support Care. 2005; 3:191-6

13. Deatrick JA, Angst DB, Moore C. Parents' views of their children's participation in phase I oncology clinical trials. J Pediatr Oncol Nurs. 2002; 19:114-21

14. Truong TH, Weeks JC, Cook EF, Joffe S. Outcomes of informed consent among parents of children in cancer clinical trials. Pediatr Blood Cancer. 2011; 57:998-1004

15. Simon C, Eder M, Kodish E, Siminoff L. Altruistic discourse in the informed consent process for childhood cancer clinical trials. Am J Bioeth. 2006; 6:40-7

16. Hinds PS, Drew D, Oakes LL, Fouladi M, Spunt SL, Church C, et al. End-of-life care preferences of pediatric patients with cancer. J Clin Oncol. 2005; 23:9146-54

17. Keusch F, Rao R, Chang L, Lepkowski J, Reddy P, Choi SW. Participation in clinical research: perspectives of adult patients and parents of pediatric patients undergoing hematopoietic stem cell transplantation. Biol Blood Marrow Transplant. 2014; 20:1604-11

18. Berg SL, Winick N, Ingle AM, Adamson PC, Blaney SM. Reasons for participation in optional pharmacokinetic studies in children with cancer: a Children's Oncology Group phase 1 consortium study. Pediatr Blood Cancer. 2010; 55:119-22

19. Miller VA, Baker JN, Leek AC, Hizlan S, Rheingold SR, Yamokoski AD, et al. Adolescent perspectives on phase I cancer research. Pediatr Blood Cancer. 2013; 60:873-8

20. Ulrich CM, Grady C, Wendler D. Palliative care: a supportive adjunct to pediatric phase I clinical trials for anticancer agents? Pediatrics. 2004; 114:852-5

21. Tomlinson D, Bartels U, Hendershot E, Constantin J, Wrathall G, Sung L. Challenges to participation in paediatric palliative care research: a review of the literature. Palliat Med. 2007; 21:435-40

22. Hunfeld JA, Passchier J. Participation in medical research; a systematic review of the understanding and experience of children and adolescents. Patient Educ Couns. 2012; 87:268-76

23. van der Geest IM, Darlington AS, Streng IC, Michiels EM, Pieters R, van den Heuvel-Eibrink MM. Parents' experiences of pediatric palliative care and the impact on long-term parental grief. J Pain Symptom Manage. 2014; 47:1043-53

24. van der Geest IM, van den Heuvel-Eibrink MM, Falkenburg N, Michiels EM, van Vliet L, Pieters R, et al. Parents' Faith and Hope during the Pediatric Palliative Phase and the Association with Long-Term Parental Adjustment. J Palliat Med. 2015;

25. Ritchie J, Lewis J. Qualitative research practice: a guide for social science students and researchers. London: SAGE; 2003

26. Hinds PS, Oakes L, Furman W, Quargnenti A, Olson MS, Foppiano P, et al. End-of-life decision making by adolescents, parents, and healthcare providers in pediatric oncology: research to evidence-based practice guidelines. Cancer Nurs. 2001; 24:122-34; quiz 35-6

27. Steele R, Cadell S, Siden H, Andrews G, Smit Quosai T, Feichtinger L. Impact of research participation on parents of seriously ill children. J Palliat Med. 2014; 17:788-96

28. Dyregrov K. Bereaved parents' experience of research participation. Soc Sci Med. 2004; 58:391-400

29. Hill DL, Miller V, Walter JK, Carroll KW, Morrison WE, Munson DA, et al. Regoaling: a conceptual model of how parents of children with serious illness change medical care goals. BMC Palliat Care. 2014; 13:9

30. American Academy of Pediatrics. Committee on Bioethics and Committee on Hospital Care. Palliative care for children. Pediatrics. 2000; 106:351-7

31. Bluebond-Langner M, Belasco JB, Goldman A, Belasco C. Understanding parents' approaches to care and treatment of children with cancer when standard therapy has failed. J Clin Oncol. 2007; 25:2414-9

32. Hinds PS, Oakes LL, Hicks J, Powell B, Srivastava DK, Spunt SL, et al. "Trying to be a good parent" as defined by interviews with parents who made phase I, terminal care, and resuscitation decisions for their children. J Clin Oncol. 2009; 27:5979-85

33. Granek L, Barrera M, Shaheed J, Nicholas D, Beaune L, D'Agostino N, et al. Trajectory of parental hope when a child has difficult-to-treat cancer: a prospective qualitative study. Psychooncology. 2013; 22:2436-44

34. Baker JN, Leek AC, Salas HS, Drotar D, Noll R, Rheingold SR, et al. Suggestions from adolescents, young adults, and parents for improving informed consent in phase 1 pediatric oncology trials. Cancer. 2013; 119:4154-61