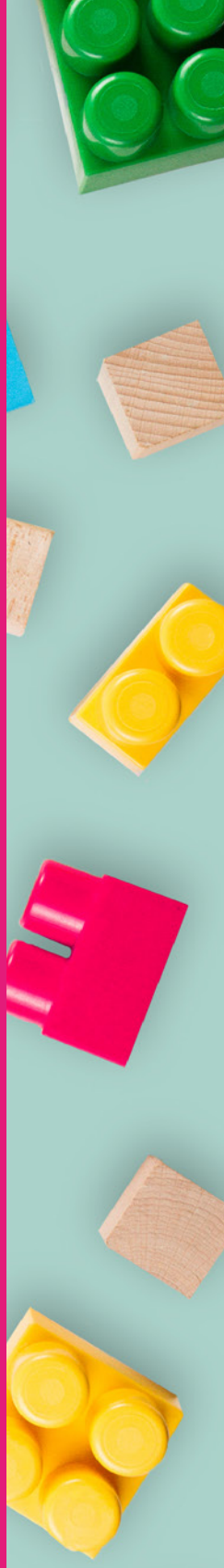
PRA Health Sciences

WHITE PAPER

Parents as Gatekeepers for Children with Cancer



Authors

Harris Dalrymple, PhD (Medicine) PhD (Law)
Executive Director, Global Scientific Affairs
Vice Chair, Center for Pediatric Clinical Development
PRA Health Sciences

Heather Peterson, RN, BSN
Pediatric Strategy Liaison, Center for Pediatric Clinical Development
PRA Health Sciences

Executive Summary

The words "your child has cancer" are words that no parent wants to hear. Despite the considerable advances made in the last 20 years or so,[1] for many, the term "cancer" equates to death. It is hardly surprising then that, when faced with this diagnosis, few parents are in a suitable state of mind to contemplate allowing their child to receive an experimental medication as part of a clinical trial.[2] This, in part, underlies the reality that few new oncology agents have been approved for pediatric use. A commonly-cited figure is that only 4 new drugs have been approved for children in the last decade, although that may not be entirely accurate.[3] However, FDA-approved oncology agents took a median 6.5 years to proceed from first-in-human to first-in-child clinical trials, demonstrating the lag in drug development in children.[4] Cancer is the number one cause of death by disease among children,[5] therefore, we must continue to work towards a better solution.

To improve cancer treatments for children, we need to conduct clinical trials. Even for drugs shown to be effective in adults, we need to work out the optimal dose and regimen for children—it's unlikely that the dose for a 17-year-old will be the same as that for a 2-year old. In the process of establishing this, we can also assess the benefit-risk ratio, which also may be different for children than for adults.[6] Pediatric cancers often differ from those in adults.[7] Unlike many cancers in adults, childhood cancers are not strongly linked to lifestyle or environmental risk factors, and only a small number of childhood cancers are caused by DNA changes that are passed from parents to their child. Some cancers are not seen in adults. For example, neuroblastoma is very rare after age 10, and retinoblastoma is extremely rare after age 20, whilst carcinomas account for 75% of adult cancers, but are very rare in children.[8] In such conditions, we have no prior data to guide us—in these situations, without clinical trials, oncologists have only their own instincts and experience to guide them when trying to treat children with a new, investigational drug.

One way of considering clinical trials of investigational drugs in children is to view the process as a series of gates through which the parents need help and support to pass, and in doing so, take their children with them. This white paper will describe the journey parents take throughout such a trial.

Gate 1: The Initial Diagnosis

Faced with a cancer diagnosis, many parents will initially be in a difficult place emotionally.[9] The ability to comprehend the diagnosis can be overwhelming, and when this is complicated with treatment plans and potential participation of clinical trial involvement, it can be too much to absorb, especially in one day. Experienced pediatric oncologists are familiar with such reactions, and will do all they can to help parents come to terms with the diagnosis, which will enable them to listen to the prognosis and understand how potential treatment will impact the family and the child's daily activities.[10] Sadly, in many cases, the medical treatment options may be limited.[11] Drugs may not have been approved to treat the type of cancer the child has, or the approved drugs may be many years old, with a combination of low efficacy rates and a poor side effect profile.[12] Even where effective treatment is available, over 95% of childhood cancer survivors will encounter significant secondary health related issues by time they reach their mid-40s due either to the cancer or, more commonly, the result of its treatment.[13] Perhaps somewhat paradoxically, in such adverse situations, the otherwise intimidating prospect of clinical trial may become the "lifeboat" for the parents as well as the child. Experienced pediatric oncologists will recognize the settings in which discussion of the "lifeboat" is appropriate, and when parents may be ready to listen to the necessary information.

Gate 2: Introducing the Trial

Despite the increasing number of clinical trials being conducted,[14] only a minority of adults have been involved in one, and even fewer have allowed their child to enroll in a trial, so the concept and processes are strange and unfamiliar. Parents feel the introduction to the trial should allow for communication necessary to become familiar with the expectations of participation. In our experience, a trained professional, together with the child's trusted healthcare provider, should be involved and engaged for support at trial introduction. Empathetic communication—explaining the trial in clear terms—is imperative for making the parent/child feel comfortable. Together with introduction of the clinical trial, basic trial landscape should be covered including certain key points, such as:

- Participation being optional
- The child's care will not be negatively affected should they choose not to participate
- Parents can change their decision to participate at any time, and they can discuss the intricacies of trial expectations with whomever they see fit and trust
- They can take the necessary time before they provide permission

There is, of course, an obvious exception related to emergency intervention trials, but these are relatively rare in oncology. In addition, qualitative research has demonstrated that the most successful trials are those with the lowest burden and fewest barriers of participation.[15] Pediatric oncologists and their staff are familiar with introducing clinical trials to parents and children when appropriate, i.e., when the child is old enough to understand. Parents may give permission for that discussion to be held with the child in ways that alleviate, or at least address, concerns and move the parents towards the nextgate, which is often the most challenging.

Gate 3: Gaining Parental Permission (Consent)

Like every other clinical trial, oncology trials must provide information to the subjects and seek their agreement to participate. In trials involving children, parents must give their permission for the child to be approached to establish whether the child would be willing to participate in the trial, and they must also give their permission for the child then to enroll in the trial, if the child wishes to do so. This process can be termed as a "consent conference" which may last over an hour and may require several sessions to thoroughly explain treatment options (both approved treatment and clinical trial options) while obtaining parental permission.[16] This is often the stage at which avoidable difficulties arise.

The information provided to parents and children must be currently approved by an Institutional Review Board (IRB) in North America or a Research Ethics Committee (REC) in other countries. In the EU, in most countries, a single REC will provide the approval for every site in the country. In the US, the position is slightly different, depending on which organization is conducting the clinical trial. For example, if the trial is run through the Children's Oncology Group (COG) the protocol will be reviewed by the National Cancer Institute (NCI) Review Board and then the local IRB, thereby providing multiple reviews of the protocol prior to approval.

The average reading age of adult in North America and Europe is around 14 years,[17] but the documents provided commonly have a higher reading age, and are frequently strewn with technically complex terminology, which is often confusing for parents to understand.[18] One study demonstrated that the average length of consent documents in oncology trials had doubled in 20 years.[19] Another study found that the average length of the consent forms in oncology trials had increased 10-fold from 1987 to 2010, and that patient understanding was inversely proportional to page count.[20]

The survey periods for both of these studies preceded the introduction of requirements relating to data privacy, which has generally resulted in the addition of three to five pages to these documents, pages, and employs pseudo-legal lingo rather than pseudo-medical jargon.

The parental information sheet (AKA Informed Consent) originally was intended to assist in the decision making process and provide a means of understanding to parents. As described above, the content often refers to legalities, including data privacy and compensation for injury, thereby taking the focus off the study expectations and easily-understood descriptions of risks and potential benefits. Several survey results have shown "parents perceive the information as overwhelming, not only in content but the amount of information they are given."[21] As a result, at the very time parents are in a highly emotional state, they often struggle to understand the information provided in such documents. While the oncology staff will willingly answer almost any questions parents might ask, parents may not be in a state of mind to absorb the answers.[22]

It is important to consider that parents may not have the basic knowledge to decide appropriate questions to ask. For this reason, the parent information sheet should be delivered in terms of the lay person comprehension to assist the parent(s) down a path to consider the terms without creating confusion.

Other than "uncontrolled" trials, such as Phase I single dose studies, or drug interaction pharmacokinetic studies, most clinical trials involve randomization. In surveys of patients enrolled into clinical trials, randomization was the topic most frequently not understood by patients.[23] Studies often comprise standard of care plus placebo vs standard of care plus investigational product. The use of the word "placebo" is poorly understood and parents fear their child will be assigned to the placebo arm or one that will later prove to lack efficacy.[24] The reasons for this are often unclear. In some cases, it may be a result of study staff trying to avoid burdening parents further, by omitting to explain what this is. In other cases, the explanation would clearly highlight the fundamental difference between clinical practice and clinical research, described further below, and site staff may conflate the two in an attempt to minimize distress to parents.

The fact that such information is approved for use by IRB/RECs does not mean that it is effective. Investing time during the design phase of such documents to make them easier to read will be well-received by parents. Often, investigation sites will be willing to suggest wording to explain procedures which has been used successfully in previous studies.

A second major issue for parents is the realization that clinical practice and clinical trials are different. The former entails finding the best treatment for the specific patient, with the primary intent of improving that patient's health and reducing suffering. The latter is concerned with the generation of generalizable data, and the obligation to the patient has become one of minimizing harm.[25] The whole point of a clinical trial is that no one knows what the outcome might be—there is "clinical equipoise," which means that genuine uncertainty exists about which treatment is better. If we knew the answer to that question, we would not need to conduct the trial.

The Research to Accelerate Cures & Equity (RACE) for Children Act, which amends and updates the Pediatric Research Equity Act (PREA), will introduce further complexity into this aspect of the clinical trial process. Until now, the description has been relatively simple: "This drug is an ABC-123 inhibitor which has been found to slow the progression of this type of cancer in adults, and for that reason we would like to try it on your child within a controlled clinical trial setting, which means your child would be randomized to treatment with ABC-123 or a control treatment (which would often be the normal standard of care)." RACE makes this description more complex. Trying to explain to anxious parents whether the trial is a "basket" or an "umbrella" design will take great care. Many clinical trial sites will have prepared visual materials to help explain this to parents and to patients, but sponsors may also wish to prepare such materials to support sites.

Gate 4: Gaining Child Assent

The purpose of child assent (agreement) is to demonstrate the child's acknowledgment of and willingness to participate in the clinical trial. Once the child reaches either an age or a functional capacity at which s/he is capable of understanding appropriately adjusted information, and can reach a judgment, the child must be asked for and give assent to enter the trial.[26] Most countries stipulate an age in legislation from which the child's assent is a necessary precondition for entry into a clinical trial. Obviously, the intellectual level of, say, a 7-year old will normally be less than that of, say, a 17-year old, and so the information provided must be tailored to the child. Commonly,

these documents are written to three reading-age ranges: 6-8, 9-12, and 13 and older. The information contained within these can be adjusted to be age appropriate. For example, children aged 6-8 years do not need to be provided with data privacy information, information relating to pregnancy, contraception or preservation of fertility, or compensation in the event of injury. All of that information will be contained in the documents given to the parents. The 9-12 age group will need to receive information relating to pregnancy and contraception. Verifiable statistics for this age group are difficult to find, but pregnancies in children aged 9-12 are often reported in local or national press. Many parents will recoil at the suggestion, and the final decision regarding the basis upon which a female subject in this age range may enter a trial resides with the sponsor. The information given to those aged 13 and above needs to be almost identical to that given to the parents, for a variety of reasons. Under European privacy law, children gain the right to control the collection and processing of their information between the ages of 13 and 16 (it varies by country). Under European clinical trial regulations, the age at which children may give consent to trial participation in their own right ranges from 14-18 years (again, this varies by country). So, including that information in the documents given to children aged 13 and above at the time of entry to the trial should equip them for future needs. The child's assent alone is not sufficient authority for the child to participate and must be accompanied by a parental/legal guardian permission.

Obviously, the child must be given an explanation of the trial according to his/her capacity to understand. In some cases, cancer being one, parents may wish the child not to be told of his/her condition, or the prognosis. The underlying principle is that of respecting the developing autonomy of the individual.[27] Therapeutic privilege (the right to withhold information which the physician adjudges would be detrimental to the patient's care, welfare, or psychological state) is not uncommon in medical practice, but its acceptability in a research setting is less clear, and may undermine the basis upon which a child has given assent (or, indeed, a parent has given permission). Accordingly, the parents need to be informed of this before giving permission for the child to be approached regarding trial participation, otherwise they are likely to be subject to therapeutic misconception (i.e., a mistaken belief that the treatment given in the clinical trial will be the best treatment for the child).[28]

Gate 5: Trial Conduct

In most oncology trials, treatment initiation entails at least one multiple-day in-patient stay. Ideally, the trial center will have facilities which enable a parent to remain with the child during that time. Sometimes, provisions for siblings may also be required. Both the child in the trial and any siblings are likely to find long periods of relative inactivity boring, and so provision for activities and entertainment are important, but parents also need to be forewarned that this situation will likely arise.

While staying in a hospital and having all sorts of tests may initially be exciting for some children and frightening for others, once the initial visits are complete, many oncology trials lapse into a routine of monthly or quarterly visits, with the same tests being run at each visit. Again, this can become tedious for children, so parents need to be prepared for this new routine.

The demands on the parents are considerable. In addition to their natural anxiety about their sick child, the parents need to ensure compliance with visit schedules, with the medication regime, and the completion of various questionnaires. The child is likely to miss a lot of schooling, and so the parents may need to arrange for support at home for the child to keep up with schoolwork, or at least not to fall too far behind. The school will need to be informed of the reason for the child's repeated absence.

When parents must care for a child who is seriously ill, it affects the entire family, including siblings.[29] Ill children may consume much of the parents' time, emotionally and physically, leaving healthy siblings in unfamiliar territory. An adolescent's healthy sibling may internalize the situation differently from a younger-aged healthy sibling. For example, they may not understand why they are treated differently or why parents must tend to the other child in such an exhaustive manner. How each sibling perceives the situation is individualized but commonly demonstrated in behaviors such as depression, guilt, anger, resentment, loss of "normal life," anxiety, and overall loss of their "identity."[30]

Particularly for adolescents, the psycho-social impacts of cancer and participating in a clinical trial can be significant. Explaining these impacts to trial participants and their parents can be challenging, particularly the reproductive aspects.

Asking adolescents for their agreement to store eggs and sperm samples for potential future use will always be an emotional discussion.[31]

Although many, but not all, clinical trial protocols address this topic, some other issues are less commonly addressed. For example, pediatric cancer patients often suffer anxiety and depression, and sometimes neurocognitive deficits, which may impact the child's re-entry to the education system, highlights a need for increased psychological assessment and monitoring.[32] The absences from school, together with any changes in physical appearance resulting from the cancer or its treatment, may impact the child's ability to make or maintain friendships.[33] Both parents and children need to be prepared for this. Many centers will be equipped with experienced child life psychologists and social services to aid with the direct impacts imposed. Parents also experience more direct impacts as a result of having a child with cancer: socio-economic status can be affected, due to employment disruption,[34] and the reduction of the child's quality of life can result in parental distress and other psychological sequalae.[35] When designing clinical trials for children, all too often the burdens trials place on parents—such as more frequent hospital visits, questionnaire completion, and medication tracking—increase those the parents are carrying anyway.

Notwithstanding the discussion regarding therapeutic misconception mentioned previously, parents and older children will be anxious to know how their cancer is responding to treatment, and here a difficult line needs to be walked. The response evaluation criteria in solid tumors (RECIST) criteria[36] are largely objective, and some parents and pediatric patients may appreciate a regular update on the development of the cancer based on these criteria. Oncology patients are often familiar with and understand clinical trial terminology.[37] This will require a significant investment of time by site staff, but if this is an approach sites are prepared to take, the return on the investment can be significant.

While retention in pediatric oncology trials is rarely an issue, the demands these trials make on parents and patients are considerable, and so all approaches which could help to maintain interest in the study are worth considering. The longer the progression-free survival, the greater the inclination to believe the experimental treatment is working, but backing up that suspicion with data will support motivation.

Gate 6: After the Trial

Most oncology protocols specify that treatment will continue until disease progression is detected, consent/assent is withdrawn, or until a specified treatment duration without progression is attained.

Disease progression—treatment failure—is never an easy discussion to have with parents, but the staff within the site will be familiar with doing this in a sensitive manner.

At Gates 2 and 3, parents will have been told that they have an absolute right to withdraw their permission for their child to continue to participate in the trial at any time. Their reasons for withdrawing permission will be many and varied. However, recognizing the growing autonomy of the adolescent,[38] investigators may face the situation of withdrawal of parental permission, in the face of a clear wish by the child to remain in the trial. In conventional medical settings, such situations are often referred to the law courts for resolution. The courts will often support the child's preference if the court is convinced that the child truly understands the consequences of his/her decision. However, conventional medicine normally involves the use of drugs, procedures, and practices which are either approved as necessary, constitute standard of care, or are in line with guidance from professional bodies. Clinical trials rarely fall within these three categories, and few sponsors appear to have anticipated such situations.

The completion of the protocol-specified treatment duration without evidence of disease progression is a situation for which sponsors can prepare. Will the investigative treatment be stopped or continued, and if the latter, on what basis? Such conversations often revolve around the regulatory or legal basis upon which the drug may continue to be supplied (e.g., named patient and compassionate use) but the requirements in various countries vary considerably.[39] Ideally, sponsors will have specified in the original protocol the course(s) which will be followed in such a circumstance, established national requirements, and made the necessary filings to regulatory authorities and IRBs/RECs in sufficient time to receive approvals for continued provision of treatment with the investigational product.

If the investigative treatment is to be stopped, then this should have been explained very clearly to the parents and the trial subject at the outset of the trial, and subsequently. Notwithstanding any requirements by regulatory authorities or IRBs/IECs, the original protocol should have contained either a clear explanation of any further assessments should there be an indication that the cancer has begun to progress.

Finally, regardless of the outcome for their own child, many parents would appreciate learning whether the investigational drug had been found to be effective. The EMA now requires the creation of lay summaries of clinical trial results, but at present, the FDA does not require lay summaries of clinical trial results to be publicly disclosed.[40] However, the greater challenge is often that of alerting the parents and ex-patients to the fact that these reports are available. Pediatric oncology trials typically last many years. The first patients enrolled into the trial may have achieved a progression-free survival period of a year or more before enrollment is even half-complete. By the time the lay report is issued, the first trial subjects may have reached the age of leaving home, their parents may also have relocated, and the investigator may have retired or moved to another institution, so an obvious route to the parents or trialists to alert them to the report may not exist. Again, planning for this type of success should begin early in the study, and the solution will not be the same in every country. In some countries, national registers exist, sometimes maintained by patient advocacy groups, which may provide a route through which to alert parents and patients.

Conclusions

Each gate of a clinical trial is a challenge in general, and when you add the inclusion of a child to the schematics, it may seem unbearable at times for parents and children to navigate. Strategies continue to emerge to aid parents in the decision-making process of trial participation, such as improved readability of the information sheet and increased use of home healthcare services to reduce the need for additional visits to study centers. The journey which the parents of a child diagnosed with cancer must take as part of a clinical trial is a long and complex one. Even if the treatment period is only 6 months long and the follow-up takes a year, the lay report for the study may be published a year after the last visit for the last patient in the study, and that patient may have been followed up for a year, so the time from study initiation to lay report may be a decade. Sponsors need to be prepared to make a long-term investment in such studies. It is unlikely that many staff will remain associated with the study for such a long period of time, so information transfer will be essential to ensure that any commitments made to sites, parents, or patients can be supported. "In order to continue to improve health care for children, clinical trials must be conducted. Investment into better evidence-based treatments for children is an investment into a better future for all."[41]

References

1. Simon, S. (2019) Facts & Figures 2019: US Cancer Death Rate has Dropped 27% in 25 Years. American Cancer Society, available at https://www.cancer.org/latest-news/facts-and-figures-2019.html. Cancer Survival Rates (2020) Nuffield Trust, available at https://www.nuffieldtrust.org.uk/resource/cancer-survival-rates.

2. See, for example, Pratt, C.B. (1991). The conduct of phase I-II clinical-trials in children with cancer. Med.Pediat. Oncol., 19:304-309; Truong, T.H., Weeks, J.C., Cook, E.F. et al (2011). Outcomes of Informed Consent Among Parent of Children in Cancer Clinical Trials. Pediat.Blood Cancer, 57: 998-1004; Robertson, E.G., Wakefield, C.E., Cohn, R.J. (2019). Piloting a parent and patient decision aid to support clinical trial decision making in childhood cancer. Psych-Oncology, 28: 1520-1529.

3. Barone, A. (2019). Approved Cancer Drugs for Children. Food and Drug Administration, available at https://www.fda.gov/media/122693/download.

4. Neel DV (2019). FDA-approved cancer drugs take more than 6 years to reach children. Eur.J. Cancer, doi:10.1016/j.ejca.2019.02.011.

5. National Cancer Foundation. (2019). Facts about childhood cancer. Available at https://nationalpcf.org/facts-about-childhood-cancer/.

6. M.A. Turner, M.A., Catapano, M., Hirschfeldc, S., Giaquinto, C. (2014). Paediatric drug development: The impact of evolving regulations. Adv.Drug Delivery Rev., 73: 2–13; Wendler, D. (2012). A new justification for pediatric research without the potential for clinical benefit. Am.J.Bioethics, 12, 23–31.

7. 7. Brian Hutzen,B., Ghonime, M., Lee, J., Mardis,E.R., et al. (2019) Immunotherapeutic Challenges for Pediatric Cancers. Mo.Ther.Oncol., 15: 38-48.

8. Dana-Farber Cancer Institute (2018). What is the Difference Between Cancer in Adults and Cancer in Children? Available at https://blog.dana-farber.org/insight/2018/09/difference-cancer-adults-cancer-children/.

9. Sultan, S., Leclair, T., Rondeau, E., et al. (2016). A systematic review on factors and consequences of parental distress as related to childhood cancer. Eur.J.Cancer Care, 25:616-637; Law, E., Fisher, E., Eccleston, C., Palermo, T.M. (2019). Cochrane Database Syst Rev., Mar; 2019(3): CD009660; Carlsson, T., Kukkola, L., Ljungman, L., et al. (2019). Psychological distress in parents of children treated for cancer: An explorative study. PLOS ONE, 14: Article Number: e021886

10. Kearney, J., Salley, C., Murial, A. (2015). Standards of psychosocial care for parents of children with cancer. Pediatr. Blood Cancer, 62: S632-S683; Last, B., van Veldhuizen, A. (1996) Information about diagnosis and prognosis related to anxiety and depression in children with cancer aged 8-16 years. Eur.J.Cancer, 32:290-294; Hocking, M., Kazak, A., Schneider, S., et al. (2014). Parent Perspectives on Family-Based Psychosocial Interventions in Pediatric Cancer: A Mixed-Methods Approach. Support Care Cancer, 22: 1287–1294.

11. Mills, C.C., Kolb, E.A., Sampson, V.B. (2017) Recent advances of cell-cycle inhibitor therapies for pediatric cancer. Cancer Res. 2017;77:6489-6498; Forrest, S.J., Geoerger, B., Janeway, K.A. (2018). Precision medicine in pediatric oncology. Curr Opin Pediatr. 2018;30:17-24; Siegel, R.L., Miller, K.D., Jemal, A. Cancer statistics, 2017. CA Cancer J Clin. 2017;67:7-30; Armstrong, G.T., Chen, Y., Yasui, Y., et al. (2016). Reduction in late mortality among 5-year survivors of childhood cancer. N Engl J Med., 374:833-842.

12. For example, Chen, C. Dorado Garcia, H., Scheer, M., Henssen, A.G. (2019). Current and future treatment strategies for rhabdomyosarcoma. Front. Oncol., Article Number: 1458.

13. National Cancer Foundation. (2019). Facts about childhood cancer. Available at https://nationalpcf.org/facts-about-childhood-cancer/.

14. US National Library of Medicine. (2020). Number of registered studies over time. Available at https://clinicaltrials.gov/ct2/resources/trends#RegisteredStudiesOverTime.

15. Greenberg, R.G., Gamel, B., Bloom, D., et al. (2018). Obstacles to Pediatric Clinical Trial Enrollment: Why Parents Refuse; Findings from the Clinical Trials Transformation Initiative. Contemp.Clin.Trials Comm., 9: 33-39.

16. Olechnowicz, J., Eder, M., Simon, C., et al. (2002). Assent observed: Children's involvement in leukemia treatment and research discussions. Pediatrics,109: 806-814; Miller, V.A., Baker, J.N., Leek. A.c., et al. (2014). Patient Involvement in Informed Consent for Pediatric Phase I Cancer Research. J.Ped.Hem.Onc., 36: 635-640; Ingersgaard, M.V., Tulstrup, M., Schmiegelow, K., et al. (2018). A qualitative study of decision-making on Phase III randomized clinical trial participation in paediatric oncology: Adolescents' and parents' perspectives and preferences. J.Adv.Nursing, 74: 110-118.

17. For Europe, see Dinis da Costa, P., Albergaria Almeida, P. Araújo, L. (2013). Reading Literacy in EU Countries: Evidences from PIRLS. European Commission Joint Research Centre, Institute for the Protection and Security of the Citizen. Available at https://publications.jrc.ec.europa.eu/repository/bitstream/JRC86217/pirls_report_final.pdf; for the USA, see Irwin S. Kirsch, I.S., Jungeblut, A., Jenkins, L., Kolstad, A. (2002). Adult Literacy in America, 3rd edition. U.S. Department of Education, Office of Educational Research and Improvement A First Look at the Findings of the National Adult Literacy Survey, available at https://nces.ed.gov/pubs93/93275.pdf. See also Davis, T.C., Williams, M.V., Marin, E., et al. (2002). Health literacy and cancer communication. CA-A Cancer Journal For Clinicians., 52:134–149.

18. See, for example, S.M. Sharp,S.M. (2004). Consent documents for oncology trials: does anybody read these things? Am.J.Clin.Oncol., 27; 570-575.

19. Berger, O., Grønberg, B.H., Sand, K., et al. (2009). The length of consent documents in oncological trials is doubled in twenty years. Ann.Oncol., 20; 379-385.

20. Nathe, J.M., Krakow, E.F. (2019). The challenges of informed consent in high-stakes, randomized oncology trials: a systematic review. MDM Policy & Practice, available at https://doi.org/10.1177/2381468319840322.

21. Jansen-van der Weide, M.C., Caldwell, P.H.Y., Young, B., de Vries, M.C., et al (2015). Clinical trial decisions in difficult circumstances: parental consent under time pressure. Pediatrics, 136: 983-992.

22. Miller, V.A., Drotar, D., Burant, C., Kodish, E. (2005). Clinician-parent communication during informed consent for pediatric leukemia trials. J.Ped.Psychol., 30: 219-229; Gessler, D., Juraskova, I., Sansom-Daly, U.M., et al. (2019). Clinician-patient-family decision-making and health literacy in adolescents and young adults with cancer and their families: A systematic review of qualitative studies. Psycho-oncology, 28: 1408-1419; Alahmad, G. (2018). Informed consent in pediatric oncology: a systematic review of qualitative literature. Canc.Control, 25: 1-8.

23. Chappuy, H., Baruchel, A., Leverger, G., et al. (2010). Parental comprehension and satisfaction in informed consent in paediatric clinical trials: a prospective study on childhood leukaemia. Arch.Dis.Child., 95: 800-804; Nguyen Thanh Tam, Nguyen Tien Huy, Le Thi Bich Thoa, et al. (2015). Participants' understanding of informed consent in clinical trials over three decades: systematic review and meta-analysis. Bulletin World Health Organization, 93: 186-198H.

24. Caldwell, P.H.Y., Murphy, S.B., Butow, P.N., Craig, J.C. (2004). Clinical trials in children. Lancet, 364: 803–811; Caldwell, P., Butow, P., Craig, J. (2003). Parents' attitudes to children's participation in randomized controlled trials. J.Pediatr., 142: 554–559; Faria, V., Kossowsky, J., Petkov, M.P., et al. (2017). Parental attitudes about placebo use in children. J.Pediatrics, 181: 272- 278.

25. Adapted from Heyd, D. Experimentation Trial: why should one take part in medical research? In: Emanuel, E.J., Crouch, R.A., Arras, J.D., Moreno, J.D. Grady, C., eds. Ethics and regulatory aspects of clinical research – readings and commentary. Baltimore: Johns Hopkins University Press; 2003. Chapter 23, p161-166.

26. Lepola, P., Needham, A., Mendum, J., et al (2016) Informed consent for paediatric clinical trials in Europe. Arch.Dis. Child.,101:1017–1025.

27. Cole, C.M., Eric Kodish, E. (2013). Minors' right to know and therapeutic privilege. Virtual Mentor, 15: 638-644; Brockman, L., Moreno, M.A. (2008). Withholding Information from an Adolescent. Virtual Mentor, 10: 496-500; Hudson, N., Spriggs, M., Lynn Gillam, L. (2019). Telling the truth to young children: Ethical reasons for information disclosure in paediatrics. J.Ped.Child Health, 55: 13-17.

28. Appelbaum, P.S., Roth, L.H., Lidz, C. (1982). The Therapeutic Misconception: Informed Consent in Psychiatric Research. Lnt.J.Law Psych., 5: 319-329.

29. Chin, W.L., Jaaniste, T., Trethewie, S. (2018). The role of resilience in the sibling experience of pediatric palliative care: what is the theory and evidence? Children-Basel, 5: Art.No.:97.

30. Hirsch, L. (2015). Caring for Siblings of Seriously Ill Children. KidsHealth from Nemours. Available at https://kidshealth.org/en/parents/sibling-care.html.

31. Lampic, C., Wettergren, L. (2019). Oncologists' and pediatric oncologists' perspectives and challenges for fertility preservation. Acta Obstet. Gynecol.Scand., 98: 598-603; Dolmans, M.M., Lambertini, M., Macklon, K.T., et al. (2019). EUropean REcommendations for female FERtility preservation (EU-REFER): A joint collaboration between oncologists and fertility specialists. Crit.Rev.Oncol.Hematol., 138: 233-240.

32. Barker, M.M ., Beresford, B., Bland, M., Fraser, L.K. (2019). prevalence and incidence of anxiety and depression among children, adolescents, and young adults with life-limiting conditions: a systematic review and meta-analysis. JAMA Pediatrics, 173: 835-844; Ruble, K., Pare-Blagoev, J., Cooper, S., et al. (2019). Parent perspectives on oncology team communication regarding neurocognitive impacts of cancer therapy and school reentry. Pediatr.Blood Cancer, 66, Art.No.: e27427.

33. Kim, B., Patterson, P., White, K. (2018). Developmental considerations of young people with cancer transitioning to adulthood. Eur.J.Cancer Care, 27: Art.No.: e12836.

34. Roser, K., Erdmann, F., Michel, G., et al. (2019). The impact of childhood cancer on parents' socio-economic situation-A systematic review. Psycho-Oncology, 28: 1207-1226.

35. Law, E., Fisher, E., Eccleston, C., et al (2019). Psychological interventions for parents of children and adolescents with chronic illness. Cochrane Database Of Systematic Reviews, Issue: 3, Art.No.: CD009660.

36. Eisenhauer, E.A., Therasse, P., Bogaerts, J. et al. (2009). New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1) Eur.J.Cancer, 45:228–47.

37. von Itzstein, M.S. , Railey, E., Smith, M.L., et al. (2020). Patient familiarity with, understanding of, and preferences for clinical trial endpoints and terminology. Cancer, 126: 1605-1613.

38. Kathleen Boykin McElhaney, K.B., Allen, J.P., Stephenson, J.C., Hare, A.L. (2009). Attachment and Autonomy During Adolescence. In Handbook of Adolescent Psychology, eds. R.M. Lerner, L. Steinberg. © 2009 John Wiley & Sons, Inc.

39. Borysowski, J., Gorski, A. (2019). Compassionate use of unauthorized drugs: Legal regulations and ethical challenges. Eur.J.Int.Med., 65: 12-16; Borysowski, J., Ehni, H.J., Gorski, A. (2019). Ethics codes and use of new and innovative drugs. Br.J.Clin.Pharmacol., 85: 501-507.

40. Barnes, A., Patrick, S. (2019). Lay summaries of clinical study results: an overview. Pharm.Med., 33: 261-268.

41. Joseph, P.D., Craig, J.C., Caldwell, P.H.Y. (2015). Clinical trials in children. Br.J.Clin.Pharmacol., 79: 357–369.

Contact Information

For further information, or to discuss any aspect of PRA's services offered in this field, please contact your Business Development Manager or the corporate office below:

PRA Health Sciences World Headquarters
4130 ParkLake Avenue, Suite 400
Raleigh, North Carolina 27612 USA

Phone: +1 (919) 786 8200
Fax: +1 (919) 786 8201
www.prahs.com