Commentary

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On the basis of their experiences in the United Kingdom, Estlin and Ablett express frustration in the preceding article over the organisational, procedural and ethical challenges faced by investigators participating in collaborative clinical trials in children with cancer. Their central message is that legislative regulations, ethical considerations, and varying national procedures have rendered the conduct of such clinical trials overly complex and burdensome, particularly with respect to the international collaboration needed for studies involving relatively small numbers of patients, informed consent and other human subject regulations, burgeoning data requirements, patient sample acquisition and processing, and information technology limitations. They indicate that more than 80% of UK paediatricians surveyed have ethical difficulties with phase I trials. They further contend that phase II trials lack ethical evaluation and that phase III trials are beset by methodological difficulties at all stages of development. They also illustrate how little research on the clinical trial process itself has been performed in paediatric oncology, and go on to plead for further studies on the clinical trial process in children and their families. They stress that these studies should include an understanding of other cultures and can be conducted in a climate of diplomacy and compromise.

On the other side of the Atlantic, the United States leads the world in the regulation of clinical trials. Never have there been more directives on informed consent [1], human subjects assurance training [2], confidentiality [3], data safety monitoring [4], adverse event reporting [5], and related policies [6]. Despite this, in studies not cited by Estlin and Ablett, Kodish and colleagues in the Children's Cancer Group (CCG) found that the informed consent process actually does little to allay anxiety or improve a sense of control in either parents or investigators [7]. In addition, disclosure of the research aspects of medical treatment rarely appears to help the family understand the distinction between conventional care and experimental treatment [8].

The frustrations are well worth it, however. In terms of years of life saved, clinical trials in children have been more successful than clinical trials in any other patient population. In addition, paediatric cancer research has paid extraordinary dividends in terms of increasing our understanding of the basic biology of cancer and life, improving treatment in adults with malignant disease, and yielding principles of therapy and advances in the treatment of other diseases of children and adults. Despite the increasing practicalities, difficulties, and ethical issues described by Estlin and Ablett, the national pediatric cancer mortality rate in the UK is declining at a linear rate [9]. In the US as well, even though the national paediatric cancer mortality rate may be slowing down [10], the cure rate, as predicted by the plateaus in the survival curves, continues to increase, with a survival rate exceeding $>80\%$ predicted for children diagnosed during 2000 [11]. Most importantly, we must keep in mind that virtually all of the progress made to date in paediatric cancer therapy has been achieved through clinical trials in young patients themselves. This, the most important reason for conducting clinical trials, must not be forgotten.

1. Challenges for clinical trials and translational research of the future

There is a critical need for more clinical trials and translational research in paediatric oncology for many reasons. Chief among them are the fact that:

- Hardly anything can be done to prevent cancer in childhood. It occurs regularly and randomly and spares no ethnic group, socioeconomic class or geographical region. Attempts to detect childhood cancer earlier at a more favourable stage have largely failed.
- Cancer develops in 1 of every 330 Americans before the age of 20 years and the incidence continues to increase in adolescents. The reason for the increase is unknown.
- Despite the decreased mortality rate, cancer is still the leading medical cause of death in both males and females from 1 to 34 years of age.
- Progress in the treatment of several paediatric cancers has been marginal, including brainstem tumours, metastatic sarcomas, relapsed acute lymphoblastic leukaemia, and relapsed non-Hodgkin's lymphoma.

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- Adolescents with cancer have not fared as well as children from the standpoint of increased survival.

The most disappointing statistic is that cancer still kills more children than any other disease despite the highly organised, dedicated national effort to overcome this grim statistic [12,13]. The second most concerning issue to this author is that adolescents and young adults have not benefited from the improvements in cancer diagnosis and treatment to the same extent that younger patients have [14], in large part due to a relative lack of participation of adolescents in clinical trials [16]. Another major problem, also not mentioned by Estlin and Ablett, is convincing bright young investigators to go into paediatric oncology.

2. Formation of a new children's cancer group based in North America

To combat these ominous trends, paediatric oncologists in the US and Canada have recently undertaken several bold initiatives, primarily in the form of a new, single cooperative group, the Children's Oncology Group (COG), that represents all children with cancer in North America. This group was formed in 2000 from four national paediatric cancer research organisations (Children's Cancer Group (CCG), Pediatric Oncology Group (POG), National Wilms' Tumor Study Group, and Intergroup Rhabdomyosarcoma Study Group) that had been in existence for a combined total of 144 years. There are several advantages to the formation of this new group:

- It means that there is now only one national organisation for the conduct of phase I, II and III trials of new therapies for cancer in children, adolescents and young adults, and for translational research on the biology of these cancers, their causes and the long-term follow-up of cured patients into adult life. It also means that more trials can be done in the same amount of time and that uncommon or rare diseases can be studied in larger groups of patients.
- The 3280 members of the COG are expected to ensure the responsible conduct of clinical trials in their patients, and to be fully compliant with the new federal regulations cited above. The COG is expected to adopt the state-of-the-art guidelines for ethics in paediatric cancer trials that were originally developed by the CCG Bioethics Committee [17].
- The COG has a specific programme for young investigators, that includes assigning a mentor to each young investigator and making available grant awards of $30 000 for five to seven young investigators annually.
- Although the US provides proportionately more public (grant) support for paediatric oncology investigations than any other country, the COG recognises that its needs exceed government funds. The COG has therefore selected the National Childhood Cancer Foundation (NCCF), a tax-exempt, public benefit, charitable foundation, as its fiscal agent and fund-raising entity to meet this additional need.

3. Summary

National and international paediatric cancer clinical trials and translational research should be made more feasible because the payback from the investment is immense, both for children and adults with cancer and other diseases. When years of life saved are considered, more *value added* can be achieved for every dollar or pound invested in paediatric cancer research than in most, if not virtually all, other cancer research endeavours. At the same time, the potential benefit must always be weighed against individual protection from research risk. The specific challenges ahead include (1) transferring the knowledge, methodologies and technologies to countries that are not so fortunate, (2) recruiting brilliant and dedicated young investigators into paediatric oncology, (3) conducting successful international clinical trials, (4) establishing a stable source of funding for national and international paediatric cooperative cancer clinical trials, (5) creating an informatics system that can link both paediatric cooperative group operations centres around the world and the institutions within each collaborative group, (6) accessing older adolescent patients who currently do not participate in cooperative group trials, (7) merging clinical trials conducted by adult collaborative groups that overlap with trials conducted by the paediatric groups, and (8) securing the support of the insurance industry and government in covering the costs of clinical trials. The COG and other national and international cooperative groups have an excellent chance of accelerating progress in the prevention, diagnosis and treatment of childhood cancer, but the benefits would be even greater if the problems identified by Estlin and Ablett were solved. We may not like the tenor of their exposition and most of us know far too well the frustrations they express. None the less, the authors have done all of us involved in clinical trials a favour by identifying the issues. Ethical considerations in the burgeoning regulatory requirements are, in general, improving the design, conduct and reporting of clinical trials in patients of all ages. Research will benefit.

References

1. Office for Human Research Protection. *What's New*. Available at: http://ohrp.osophs.dhhs.gov/whatsnew.htm (accessed 26 January 2001).
2. Human Protections Administration. *Human Subject Assurance Training*. Available at: http://137.187.172.201/cbttng_ohrp/default.asp?CBTID=2 (accessed 26 January 2001).
3. http://www.nci.nih.gov/scienceresources/announcement/conf-intro.html
4. National Institutes of Health. *Further Guidance on a Data and Safety Monitoring for Phase I and Phase II Trials*. Available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html (accessed 30 January 2001).
5. http://ctep.info.nih.gov/AdEERS/AdEERS%20CBT%20v3.0/welcome.html
6. Announcement of the final PHS policy on instruction in the responsible conduct of research (RCR) and discussion of public comments. Available at: http://ori.dhhs.gov/html/programs/announcement.asp (accessed 30 January 2001).
7. Kodish ED, Pentz RD, Noll RB, *et al*. Informed consent in the Children's Cancer Group. Results of preliminary research. *Cancer* 1998, **82**, 2467–2481.
8. Levi RB, Marsick R, Drotar D, *et al*. Diagnosis, disclosure, and informed consent: learning from parents of children with cancer. *J Pediatr Hematol Oncol* 2000, **22**, 3–12.
9. Craft AW, Parker L. Letter to the Editor — ominous trend in childhood cancer mortality? *Med Pediatr Oncol* 2001, in press.
10. Bleyer WA. United States pediatric cancer mortality: an ominous trend? *Med Pediatr Oncol* 2001, in press.
11. Bleyer WA. The past and future of cancer in the young. *Pediatr Dent* 1995, **17**, 285–290.
12. Bleyer WA. The U.S. pediatric cancer clinical trials programmes: international implications and the way forward. *Eur J Cancer* 1997, **33**, 1439–1447.
13. Bleyer WA. The impact of childhood cancer on the United States and the world. *CA Cancer J Clin* 1990, **40**, 355–367.
14. Bleyer WA. The adolescent gap in cancer treatment. *J Registry Management* 1996, **23**, 114–115.
16. Bleyer WA, Tejeda H, Murphy SM, *et al*. National cancer clinical trials: children have equal access; adolescents do not. *J Adolesc Health* 1997, **21**, 366–373.
17. Emanuel L, DeRenzo E, Fleischman A, *et al*. *Report from the External Committee on Conflict of Interest, Children's Oncology Group*. A copy may be obtained from Anita Khayat, PhD, Executive Officer, COG, PO Box 60012, Arcadia, CA 91066–6012, USA.