

Improving cancer care for children and young people 4

New policies to address the global burden of childhood cancers

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Childhood cancer is a major global health issue. Every year, almost 100 000 children die from cancer before the age of 15 years, more than 90% of them in resource-limited countries. Here, we review the key policy issues for the delivery of better care, research, and education of professionals and patients. We present a key list of time-limited proposals focusing on change to health systems and research and development. These include sector and system reforms to make care affordable to all, policies to promote growth of civil society around both cancer and Millennium Development Goals, major improvements to public health services (particularly the introduction of national cancer plans), improved career development, and increased remuneration of specialist health-care workers and government support for childhood cancer registries. Research and development proposals focus on sustainable funding, the establishment of more research networks, and clinical research specifically targeted at the needs of low-income and middle-income countries. Finally, we present proposals to address the need for clinical trial innovation, the complex dichotomy of regulations, and the threats to the availability of data for childhood cancers.

Introduction

In 1980, the World Development Report¹ emphasised that developing countries are home to 78% of the global population, but to 86% of the world's children. The proportion of children in developing countries is expected to increase to more than 90% by 2030. Although infectious diseases are much more prevalent than cancer in developing countries, more deaths are caused by cancer worldwide than by HIV infection, tuberculosis, and malaria combined; cancer incidence is higher in developing countries (147 000 cases per year) than in developed countries, and is growing because the populations in these countries are younger and expanding.² As a result, up to 2% of all cancers in developing countries arise in children, whereas in Europe and North America, childhood cancers constitute less than 0.5% of total incident cases. The essential policy issues framing the global care agenda for children with cancer are not only those intrinsic to paediatric oncology, but—particularly in developing countries—are also a product of a country's stage of economic development, its ensuing patterns of disease, and the sociopolitical constructs that affect health (figure 1).³

According to estimates by the International Agency for Research on Cancer for 2008, almost 100 000 deaths before the age of 15 result from cancer every year, and more than 90% of these deaths occur in low-middle income countries (figure 2).² With continued socioeconomic development, the proportion of deaths from cancer is likely to increase in developing countries, especially in young people. Mortality is high in developing countries—80% of young cancer patients in Africa die, including in countries with more developed health systems such as South Africa. Available data probably underestimate the burden of childhood cancer in

developing countries because the patterns of occurrence suggest that many patients die from undiagnosed cancer.

Nowadays, about 80% of children with cancer in high-income countries survive.⁴ However, in resource-limited settings, many cases of cancer are detected too late for effective treatment, and are compounded by comorbidities (especially malnutrition), affordability, and restricted access to treatment and care.⁵ The burden and range of childhood cancers varies substantially between countries. Global policies to address the care, education, and study of children with cancer and their families need to deal with both commonalities—eg, the effect of legislation on childhood cancer research and development—and the specific contexts of where these children live. Because socioeconomic, demographic, and

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This is the fourth in a **Series** of four papers about improving cancer care for children and young people

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Figure 1: Policy issues surround the struggle to improve childhood cancer survival

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political circumstances vary widely in developing countries, effective cancer treatment for children will need strategies that are adapted to individual countries with limited resources. The policy myth that developing countries cannot afford to treat children with cancer needs to be debunked. High cure rates in children result in many potential years of life saved, and for some childhood cancers, such as Burkitt's lymphoma and Wilms' tumour, affordable treatments can be highly effective when given appropriately.⁶ Formal economic evaluation, by use of quality-adjusted life-years, has shown that treatment of cancer in children is a very cost-effective investment,^{7,8} particularly for cancers such as Burkitt's lymphoma and acute lymphoblastic leukaemia, which are curable in children.

The quantity and quality of statistics describing burden of disease in developing regions vary. In Africa, only three countries—Mauritius, South Africa, and Egypt—provide cancer mortality statistics to the WHO mortality database, and only about 1% of the African population is covered by reliable population-based cancer registries providing data on cancer incidence (figure 3).⁹ The population data—which are needed to produce incidence and mortality rates—are not available or are insufficient; therefore, the statistics are based on little real data. Existing population-based cancer registries are the forerunners of the cancer control plan, and should therefore receive wide-ranging support to continue providing unique and indispensable information about

cancer burden.¹⁰ Despite resource limitations, several middle-income countries—eg, Argentina, South Africa, and Iran—have implemented national population-based cancer registration for children, with support from non-governmental organisations in some cases.¹¹

In high-income countries in the past few decades, the most substantial gains in outcomes have been in childhood cancers. 5-year survival has increased from less than 30% in the 1960s to about 80% in the 2000s for all childhood cancers combined.^{12,13} The most important reason for this achievement is the integration of care and research in paediatric oncology; however, serious policy issues exist—eg, the future sustainability of research and development, integrated care networks, and the effect of regulations. We look at the issues and solutions from the other papers in this Series^{14–16} and propose solutions for all children with cancer for the next decade, irrespective of where in the world they live.

High-income countries: changing the policy landscape

Outcomes in children in high-income countries have substantially improved, but have varied with cancer type and geography.¹⁴ Despite an overall improvement in childhood 5-year survival,^{12,13} several solid cancers are still refractory to treatment. As discussed by Vassal and colleagues,¹⁶ this lack of response is partly attributable to a lag in the scientific understanding of these types of cancer, but also to the translation of adult research and development into the paediatric setting. Importantly for policy makers at the national and supranational level, Pritchard-Jones and colleagues¹⁴ state that improvements in efficacy of present regimens and treatment approaches are reaching their limit, and, despite substantial improvements in outcomes, we are a long way from curing all children with cancer. Furthermore, even for the children saved by present approaches, long-term toxicity and the associated effects on future health remain important.¹⁷ The risks include continuing excess mortality, second primary neoplasms, neurocognitive defects, cardiovascular disease, other organ dysfunction, and the psychosocial effects of disease and its treatment on the patient and their family.¹⁸ The policy environment for adults who survived childhood cancer needs to be reviewed, irrespective of any health consequences. Survivors aged 30–50 years have much the same general indicators of economic achievement and insurability as do people in the same age group who did not have cancer as children.¹⁹ But despite this, survivors in this age group are denied entry into the military and can have applications for life insurance rejected. Survivors aged 20–29 years are worse off than those who have not had cancer in several areas including educational achievement, employment, workplace and social relationships, and the ability to obtain health and life insurance.

Although we have the knowledge and methods to deliver excellent outcomes in many childhood cancers, the

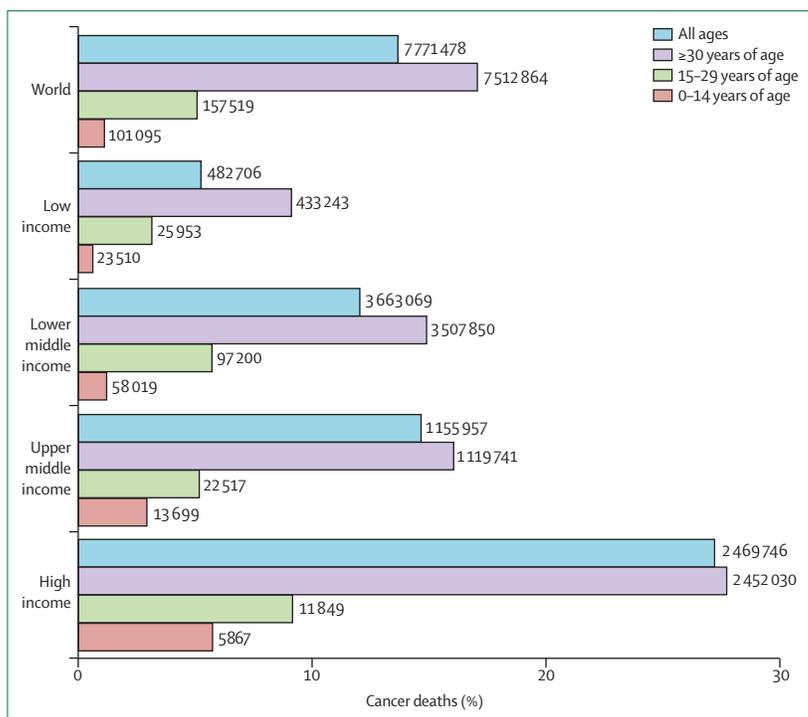


Figure 2: Cancer deaths as a percentage of total deaths, 2008

Actual numbers of cancer deaths are shown next to the bars.² WHO, Health Statistics and Informatics Department, World Health Organization, Geneva, Switzerland, 2011. <http://www.who.int/evidence/bod> (accessed Nov 21, 2012).

differences in outcomes between more and less affluent populations—irrespective of whether these are in high-income or low-income countries—is concerning. In developing countries, one of the strongest determinants of childhood mortality is the socioeconomic class of parents (figure 4).²⁰ In high-income settings, differences in geographical outcome fell between 2005 and 2009; however, childhood cancer mortality is more than 20% higher in central and eastern Europe than in the rest of Europe (figure 5).²⁰ To close this gap, the underlying reasons for the divergence need to be understood, and social and health policies need to be introduced. Attempts to help with transnational clinical research in Europe have unintentionally had negative consequences.²² Paediatric oncology groups from several central and eastern European countries were involved in international clinical trials before their countries joined the European Union (EU); almost all of the front-line treatments involved the off-label use of long established medicines that were out of patent. This situation was generally accepted by regulatory authorities, and the trials were seen as obligatory standards for the treatment of childhood cancer. However, implementation of European directives led to the overinterpretation of some regulatory requirements, without any funding to support the infrastructure changes necessary for compliance. Both research-active care networks and the viability of the care centres were adversely affected. For example, Polish paediatric oncology centres are not currently able to open any new academic clinical trials because the universities do not have the resources to meet the responsibilities assigned to the sponsor role by the Polish Government.²³ Very little government or philanthropic funding is available to support cancer care in these countries.²⁴ From a policy perspective, the crucial work is to attempt to revise European clinical trials legislation and provide advocacy, such as the European Society of Paediatric Oncology's promotion of national support for childhood cancer research.

Although comparable statistics are available in high-income countries, funding cuts and unjustified requirements on data confidentiality pose a challenge to established cancer registries. National population-based cancer registries should be advocated for childhood cancers because of their rare occurrence, centralised treatment, internal migration, data quality, and cost considerations, as recommended by EURO COURSE ERA-Net. To improve interpretation of follow-up and outcome data, clinical trial groups or consortia can enhance the quality of their data and enlarge their database with clinically relevant information. Additionally, precise statistics can help to identify gaps and outline directions for improvement—further reduction of mortality, extension of long-term survival, and limitation of treatment-related late side-effects.²⁵ Registries are not just important in high-income countries, and policy makers can learn from good models being implemented in emerging economies such as South Africa.²⁶

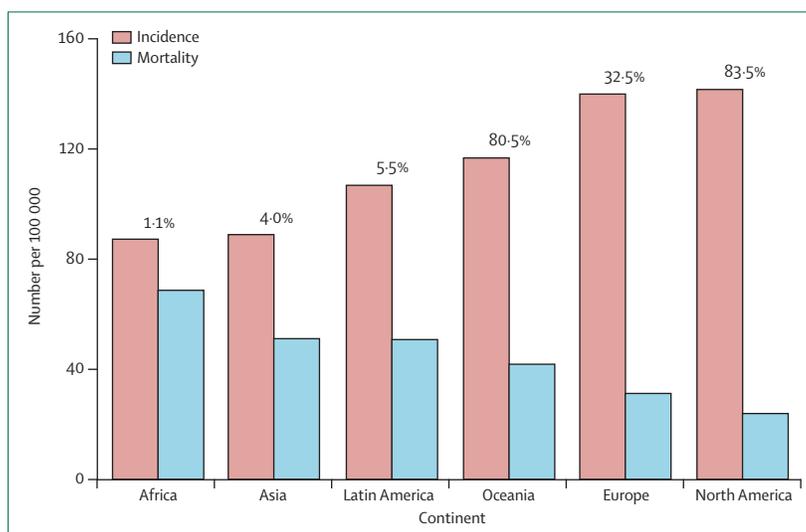


Figure 3: Incidence and mortality rates of childhood cancer, and percentage of population covered by cancer registries

Percentage figures above the bars are the percentage of the population covered by cancer registries. Reproduced with permission from Eva Steliorova Foucher.

Why have the cancer communities in high-income countries been so successful in improving outcomes in the past 30 years? One of the major lessons learnt has been for the care and research communities to organise themselves to deliver a continuously innovating system of care, with research fully integrated into clinical pathways. Innovation in the organisation of care in high-income countries has enabled the localisation and effective networking of appropriate expertise, data collection, and research. Clinical trials have also had an important role in the improvement of outcomes; the accrual rate is an order of magnitude greater for children than for adults in high-income countries, and enrolment on available clinical trials at first diagnosis has become the standard of care—an important point often not acknowledged by policy makers. The effective management of children with cancer needs long-term commitment from both health-care professionals and federal authorities to support research and care networks. The gains in outcomes should be seen in the context of other major issues, and drawbacks that arise as health-care and political systems change. In terms of policy, high-income countries still need continuous vigilance and development.

Low-income countries: improving outcomes

The burden and effect of childhood cancers in developing countries is complex; level of income, social indicators (eg, general health and education), vulnerability and risk, and sociopolitical access all play a part.²⁷ Poverty affects health and mortality at all ages, but particularly children, including those children from less affluent backgrounds in high-income countries.²⁸ As well as the direct effect of poverty, low-income countries have poor health-care provision, which means that few special cancer centres

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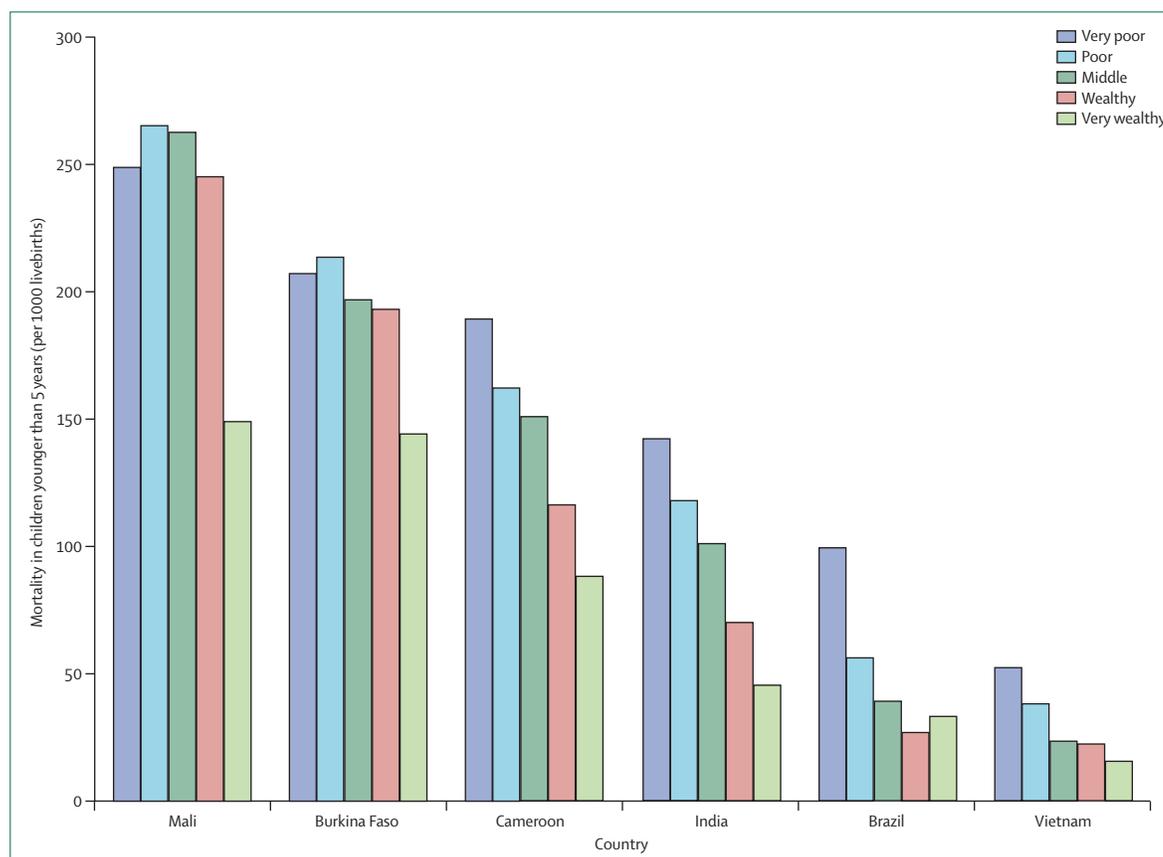


Figure 4: Mortality in children younger than 5 years per 1000 livebirths by wealth quintile, in six developing countries
Data are from demographic and Health Surveys survey data from 1996–2004.

For the Institute for Health Metrics and Evaluation Demographic and Health Survey <http://www.healthmetricsandevaluation.org/ghdx/series/demographic-and-health-survey-dhs>

are available, and if they are, they are likely to be a long and expensive journey away. 80% of people in Africa have no access to radiotherapy, cancer surgery, or the infrastructure needed for the basic delivery of cancer care.²⁹ Sufficient numbers of health-care workers and adequate levels of financial capital to bring health care to all do not exist. Such substantial intrinsic hurdles seriously compromise the development of services for children with cancer. From a policy perspective, catalytic programmes are needed to overcome this inertia.³⁰ Twinning is extremely important; the term encompasses the engagement of centres in high-income countries with developing countries, but also more regional programmes such as the links between Northern and South Africa with sub-Saharan Africa.³¹

Developing countries can be optimistic for the future. Social and health conditions are improving in many parts of the world—eg, growth in per-person private consumption in developing countries increased from 1.4% per year between 1980 and 1990, to 2.4% between 1990 and 1999, and the percentage of people living in extreme poverty (ie, less than US\$1 a day) fell from 28% in 1987 to 23% in 1998, and 19% in 2009. Policies to increase social capital—ie, the development of social relations and

networks that produce strong societal bonding, mutuality, and solidarity—around children with cancer will play a major part in the delivery of better access and services.³² While patients' organisations and advocacy movements are a young social phenomenon in many developing countries, the drive to create them has been led by the childhood cancer community in many parts of the world. Wilkinson³³ stated that social capital is essential for the enhancement of equitable service performance through the engagement of civil society to advocate for services and hold providers to account. The effect of poor social capital on outcomes in children with cancer is pronounced. In one study of outcomes in children with acute lymphoblastic leukaemia in Indonesia, 47% of parents from deprived areas refused or abandoned treatment compared with 2% from affluent areas.³⁴ The same study suggested that strong social hierarchical structures hindered communication with doctors, and resulted in insufficient parental understanding of the need to continue treatment.

Infant mortality rates fell from 107 to 59 per 1000 livebirths between 1970 and 1999, and adult literacy rose from 53% in 1970 to 74% in 1998.³⁵ These changes are important because a lack of young people who are

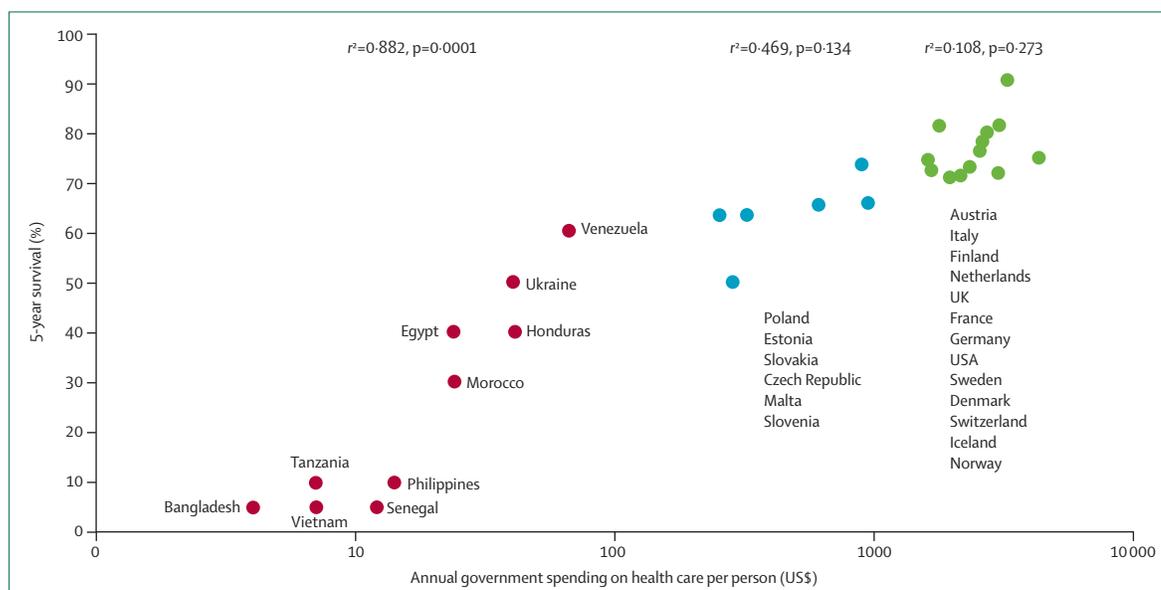


Figure 5: Relation between annual governmental health-care expenditure and childhood cancer survival, 2008

5-year survival for all countries in red (from Bangladesh to Venezuela) were not measured, but derived from a survey of health professionals. Reproduced with permission from reference 21.

qualified to attend university limits the capacity for training health-care workers. Cancer care depends on a range of professions, including engineers, pharmacologists, and many specialists such as ophthalmologists, radiologists, and pathologists, in addition to the oncology community. The introduction of education and social capital policies in developing countries, and the development of dedicated units for treating children with cancer, will be essential for the delivery of adequate childhood cancer services.³⁶

The most important determinant of outcome for a child with cancer is where he or she is born. In south Asia, four out of ten households (more than 500 million people) are in poverty, and infant and child mortality varies widely between different regions. In our health lifecycle, childhood is one of the most vulnerable periods with respect to disease and ill health because of biological and socioeconomic immaturity; therefore, children suffer the consequences of poverty more than adults.³⁷ Parental income is an important determinant of child cancer inequalities across countries, but other determinants—eg, education, the political situation, and environment—are also important.³⁸ Average country income has a strong indirect effect on maternal education, which has a major influence on child health.³⁹ Maternal education is closely related to a woman's control over household issues, including awareness of health issues. Additionally, accessibility to health services is very important; countries that have achieved good health at low cost also had health systems that were free at the point of delivery and easy to access. Unsurprisingly, high maternal mortality rates are associated with regions of high childhood cancer mortality. Differences between regions in female access

to education also affect the ability of countries to deliver improved childhood cancer services—eg, India has a 16.6% difference between the school enrolment of girls and boys aged 6–14 years. In Niger, the enrolment rate of boys is 41% higher than that of girls. The development of health policy is as important as are cancer-specific initiatives in developing countries.

New policies to support research into childhood cancer

A new paradigm for drug development

Drug development for cancer has progressed from cytotoxic regimens to molecularly targeted agents.⁴⁰ Molecular dissection, targeted agents, and biomarker codevelopment have shaped and driven adult oncology, and are now being applied to some childhood cancers previously defined in anatomical terms—eg biomarkers are available for medulloblastoma and neuroblastoma.⁴¹ However, increased understanding of the complex biology of certain cancers, and their subsequent molecular characterisation, has not been easily or quickly translated into improved outcomes. This shortfall might be an issue of scientific progress in the elucidation of complex biological pathways in childhood cancers, or something more fundamental—eg, higher-resolution pictures of cancer might not necessarily translate into improved outcomes. Likewise, Vassal and colleagues⁴⁶ point out that only some of the identified targets might be treatable with present technologies. Furthermore, the economic ability to develop drugs for rare targets is a serious policy issue. Although molecular characterisation of adult malignant disease has paved the way for novel drug development, many of the paediatric targets differ

from those in adults. Big challenges remain in the translation of the science of childhood cancers into new drugs, and specific programmes and funds are needed to drive this fundamental research.⁴² Moreover, the short-term and long-term toxicity profiles of these new agents are very unpredictable.

Importance of clinical trials

Clinical trials have had, and will continue to have, an essential role in the development of novel drugs for children with cancer. The high rates of recruitment to clinical trials contributed to one of paediatric oncology's greatest achievements—a substantial improvement in survival. However, as the biology of childhood cancers becomes better understood,⁴³ and more targeted drugs are developed, the paediatric research community needs to embrace novel trial designs and biomarker codevelopment strategies.⁴⁴ Other crucial areas for evolution are the harmonisation of response definitions, and the use of response as a continuous variable. Importantly, for development of cooperative clinical trials between North America and Europe, harmonisation of procedures and biomarker development is urgently needed.⁴⁵ Furthermore, the codevelopment of biomarkers found from biospecimen collection and the addition of various novel imaging methods in several trial settings need to catch up with the adult field. Beyond the issue of trial design development, the division between clinical trial outcomes, overall service outcomes, and service improvement processes is a problem. Paediatric oncology research progressed quickly during the 1980s and 1990s because the boundary between research and service improvement was less obvious than it is now. As clinical trials develop and become more focused because of the molecular characterisation of cancers, inclusion criteria will become more rigorous and, therefore, will exclude many patients. To ensure outcome is not compromised, patients who do not enter trials should undergo the same rigor of investigation and staging of disease as do patients in clinical trials. Countries should ensure that quality outcomes are monitored both nationally and for each treating centre.

Treatment of children with cancer in the foreseeable future will continue to rely on regimens using chemotherapy and radiotherapy,⁴⁶ both of which have serious immediate and long-term issues of toxicity.⁴⁷ Academic programmes and trial investigators need to better prospectively explore cohorts of survivors, and to propose adapted care for adults with long-term effects of their childhood cancer treatment. This approach will include more research into mitigation of the effects of toxicity from present regimens and novel targeted agents⁴⁸ and guaranteed long-term follow-up of survivors. This latter point is particularly important as current pharmacovigilance requirements provide little mandated follow-up data for new medicines.

Collaboration and funding

In view of the increased biological, organisational, and regulatory complexity, and the diversity of research and development in childhood cancers, what new models are needed? Vassal and colleagues remind us that “Time is an issue. Speed up new drug development for our children”.¹⁶ Therefore, new models of partnership and collaboration are as much about delivering new solutions quickly as they are about innovation. In high-income countries, the paediatric research and development community have long had well organised collaborations between patients, parents, clinicians, and scientists.⁴⁹ However, the interface with the adult drug development community and the pharmaceutical industry still has major gaps.

The continuation and advancement of research into children with cancer depends on long-term, sustainable funding; however, evidence suggests that paediatric research and development is reliant on short-term, unsustainable funding (figure 6). Despite new initiatives, this short-termism is a major concern. The US National Cancer Institute and other parts of the National Institutes of Health have dominant roles in North America, and fund almost half of all paediatric oncology research in the USA.⁵⁰ In Sweden, charities and endowed foundations fund more than 40% of research. Other nationally prominent European funders include the *Associazione Italiana per la Ricerca sul Cancro* in Italy, *Deutsche Krebshilfe* in Germany, the Netherlands Cancer Society, and Cancer Research UK. The European Commission funds only 7% of childhood cancer research. The support of paediatric oncology research by the EU is a positive step, but it is inadequate for the scale of the problem. Furthermore, at the national level, funding is too low or too unstable, with much activity reliant on short-term funding. National and international funding needs to be more sustainable and coherent.

The role of the pharmaceutical industry

What is the best way to identify effective treatments for childhood cancers? In view of the complex and heterogeneous nature of these cancers, the trend in the past few years for industry to drive the development of clinical research plans contrasts with the need for broad research and development partnerships that can deal with complex biology and drug development. Companies are developing research plans to meet regulatory obligations related to the drugs that they are developing for adult cancers. This trend takes the primary responsibility for research direction away from the larger paediatric oncology community, and also tends towards the fragmentation of childhood cancer clinical research activities—as opposed to the cooperative, unified clinical research activities that are needed in view of the small numbers of children with specific cancer types. Thus, the long-term effects of this trend raise serious concerns.

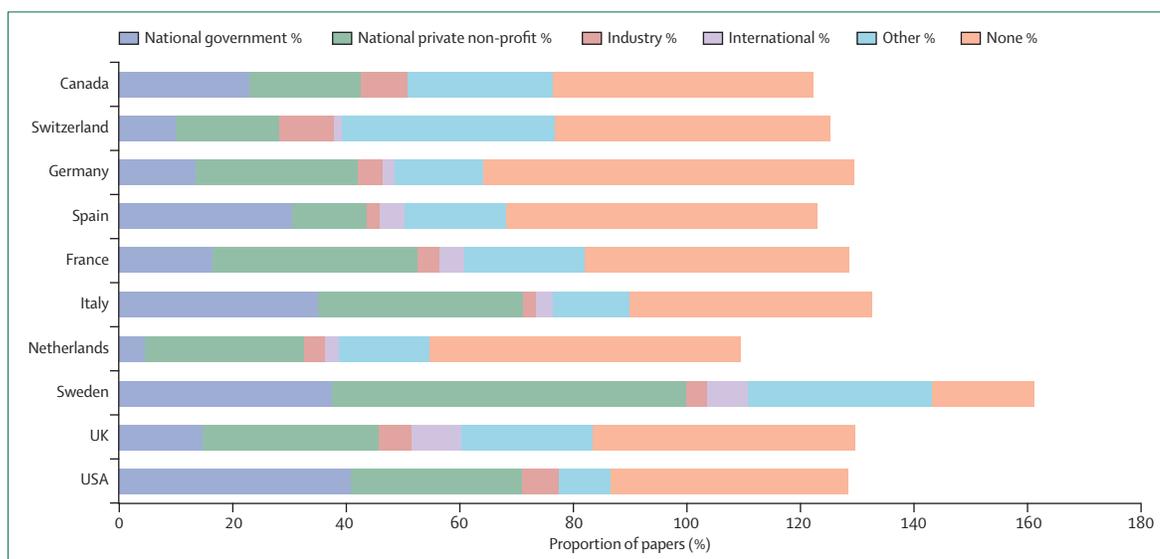


Figure 6: Mean percentage support for paediatric oncology research from various funding sectors in ten selected countries, 1997–2000 and 2005–2008
 Graphs show combined totals for papers published in the two time periods. Percentages add to more than 100% because of multiple funders on some papers.
 Reproduced with permission from Kathy Pritchard-Jones and colleagues.⁵⁰

Regulation

Regulation affecting research and development in childhood cancers has had both adverse and beneficial consequences. For example, in Europe, the Clinical Trials Directive has had devastating effects on several publicly funded clinical trials, particularly those focused on childhood cancers. However, these international clinical trials have delivered, and will continue to, deliver excellence in care and new treatment strategies.⁵¹ The Clinical Trials Directive has almost quadrupled costs and led to substantial delays and even the discontinuation of trials.⁵² Additionally, data protection legislation (the 1995 Data Protection Directive in Europe and the Health Insurance Portability and Accountability Act in North America) has negatively affected the ability of the paediatric research community to share data internationally, and hindered the activity of essential registries. In Europe at least, policy makers seem to find it difficult to create legislation that promotes, rather than inhibits, life-saving research. A planned revision to the European Data Protection Directive is causing major concerns among cancer registries and researchers that this work will be discontinued.⁵³

Another regulation issue was the attempt to improve pipelines of novel compounds by regulatory mechanisms to drive crossover of adult new molecular entities to the paediatric setting. In 1997, the USA, and in 2007, the EU, introduced regulations for improved drugs for children with cancer. In the USA, two pieces of legislation, the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act cover the need for paediatric information for approved drugs. These regulations have substantially affected drug development for children with cancer, and other childhood diseases.⁵⁴ All pharmaceutical companies must now

consider paediatric oncology in their development programmes. However, too many companies view childhood oncology as a regulatory requirement to comply with, rather than having a biology-based research and development approach that integrates into the paediatric setting.⁵⁵ Furthermore, plans for drugs to meet regulatory requirements in children are inherently drug-focused rather than disease-focused; as a result, the clinical trials proposed for a particular drug might be of low clinical relevance or the eligible paediatric patients might be extremely rare. Clinical cancer research should maintain disease-focused prioritisation of clinical research led by the paediatric oncology expert community rather than drug-focused prioritisation led by pharmaceutical companies and regulatory authorities.

In low-income and middle-income countries, several types of research are needed for progress. Because local conditions change as new infrastructure and personnel become available, the adaptation of treatment regimens to local conditions is a continuous project. Therefore, a system of continuous quality improvement should become habitual in developing countries, so that clinicians can cure as many children as possible with existing resources, while simultaneously improving knowledge and infrastructure to increase future cure rates. This model is much like the one used in high-income countries, where enrolment in a clinical trial is deemed standard care, but differs in that each centre—or region, if conditions are similar across the region—must undertake its own implementation research to identify gaps and areas for improvement. For example, the Central American Paediatric Haematology-Oncology Association, which comprises eight centres in seven countries, uses uniform protocols

that have been adapted to the local setting, and carefully monitors outcomes. These outcomes include death from treatment toxicity and abandonment of treatment, which are the two most common causes of treatment failure for children with cancer.⁵⁵ Twinning programmes for individual centres, and regional networks of similar

Proposal	Comments	Difficulty	When achievable
Health systems and health policy			
Different outcomes between children from affluent and deprived backgrounds	Research into the inequalities in outcomes of childhood cancers and the development of new policies.	High complexity	Medium term
Insufficient affordable cancer care for most children in developing countries	New health-sector reforms that target the health of poor people, including improvements in tax to finance systems, reduction in cost of services to poor people and social insurance models, and policies that deliver services with equity and that have built in monitoring and evaluation targets. Develop a national childhood cancer plan with designated hospitals certified to provide care, rapid referral systems, and access to care for the entire population.	High complexity	Medium term
Insufficient civil society and advocacy to deliver current Millennium Development Goals relevant to child health	Promote the growth of civil society in low-income countries to support the financial situation of existing childhood cancer providers, with the International Confederation of Childhood Cancer Patient Organisation to support and develop national organisations.	High complexity	Medium term
Insufficient public health systems in developing countries	Improvements in policies that help a variety of patients with acute and chronic illnesses. For example: societal health literacy; community and primary care; primary, secondary, and tertiary infrastructure and personnel training; laboratory services (particularly microbiology); infection control programmes; blood banking; diagnostic imaging; and paediatric surgery. Improvements in services specific to cancer care. For example: pathology, chemotherapy, and radiation treatment.	High complexity	Long term
Insufficient childhood cancer registries in many countries	Government mandated and supported programme to create registries. Policy makers should support institutional registries through twinning activities—eg, the Paediatric Oncology Network Database initiative with St Jude Children's Research Hospital, Memphis, TN, USA—as a first step to improvement in national cancer intelligence.	Easy to deliver	Deliverable now
Poor remuneration of health-care professionals working in the public sector	Specialisation of multidisciplinary health-care professionals needed to treat cancer in children and adolescents should be recognised and appropriately remunerated alongside career development.	Easy to deliver	Deliverable now
Research and development			
Insufficient sustainable funding mechanisms in all countries	Government and philanthropic funders to create long-term core infrastructure research and development funds. Increased strategic planning between national and international funders of research and development. Dedicated low-income and middle-income research and development funding streams.	Easy to deliver	Deliverable now
Slow progress in reduction of long-term toxicity of treatments	Create and fund national and international collaborative programmes in this area.	High complexity	Medium term
Establish and strengthen regional, national, and international professional networks	Create more discipline-specific networks (eg, pathology, surgery, and oncology), and disease-specific networks—eg, Burkitt's lymphoma (International Network for Cancer Treatment and Research), Wilms' tumour, neuroblastoma (Global Neuroblastoma Network)	Medium complexity	Medium term

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Proposal	Comments	Difficulty	When achievable	
(Continued from previous page)				
Clinical research specifically addressing cancer care needs in low-income and middle-income countries	Should include, but not be limited to, the development of clinical research and development protocols that study adapted treatment regimens, adapted supportive care strategies, abandonment prevention strategies, cost-effectiveness of alternative strategies for diagnosis, staging, risk stratification, treatment, and follow-up.	The ability to develop and carry out more clinical studies in low-income and middle-income countries is related to the funding available to train and develop research personnel.	Medium complexity	Deliverable now
Innovation in clinical trials	Research and regulatory communities should develop a range of policies to improve harmonisation of methods of clinical trial procedures, including a biospecimen policy and the application of novel designs and statistical methods.	Despite regulatory divergence between Europe and North America, major steps have already been taken to bring protocols together, and novel statistical methods are now available for use in the paediatric setting. Efforts are already underway in Canada—eg, the efforts of the major research funders the Canadian Cancer Research Alliance to urge the government body, Health Canada, to interpret the regulatory laws in a more practical and less onerous way to reduce the expense and time to carry out trials	Easy to deliver	Medium term
Innovation in collaborative organisational design for research and development	Pan-community models of collaboration (parents, academia, industry, and regulators) should commit to medium-term and long-term partnerships to deliver the next generation of innovations. Harmonisation between procedures and processes between EU groups (eg, ENCCA) and North America (COG) to encourage collaboration and speed up the development and delivery of advancements in treatment. Incorporation of regional networks of centres in low-income and middle-income countries to provide access to up-to-date treatments and to greatly increase the number of patients able to participate in clinical research and provide samples for translational research.	The pharmaceutical industry should positively engage with the paediatric research and development networks to create a new collaborative model that brings funding, and new molecules and biomarkers, into the existing clinical trial networks.	Easy to deliver	Deliverable now
Threats to availability of data on cancer burden	Legislatively mandated programme to create or sustain population-based cancer registries, ideally with national coverage for childhood populations. To avoid bias, should not need informed consent or one-way encryption of the identifying data for population-based cancer registration. Relieve constraints on publication of grouped cancer data to encourage research for the benefit of future patients. Transnational support to create an international childhood cancer survivor registries research programme that builds on existing structures is urgently needed.	Ensure data protection requirements do not jeopardise the ability for clinical trial groups or national health services to share data for pooled analyses that contribute to improved patient outcomes.	Medium complexity	Medium term
Regulatory frameworks	All national and international legislative mechanisms (eg, EU 27) should have formal mechanisms in place to include childhood cancer research within any impact assessment. Additionally, policy makers and regulators urgently need to positively engage with the clinical trials and population-based research communities as current legislation is reviewed and updated. Regulators should consider several additional improvements to paediatric investigation plans: consideration of the mechanism of action of drug rather than the adult condition; reconsideration of the waiving process; improved consideration of what is done and planned in a given paediatric cancer through drug development strategies established for each disease; development of paediatric investigation plans that address several targets from different companies for the same disease; and developing mechanisms within the paediatric regulatory framework that prioritise unmet clinical needs, led by the paediatric oncology community in partnership with parents and industry.	..	Easy to deliver	Medium term

Table: Policy priorities for the global childhood cancer agenda

centres, provide the forum for international mentoring, development of regional expertise, and generation of generalisable knowledge that will help others who treat children with cancer.²¹ The support of twinning programmes and regional networks—and holding them accountable for measurable results—could transform cancer care, provide the platform to integrate new drugs and targeted treatments on a global scale in the intermediate term, and lead to excellent cure rates for all children everywhere in the long term.

Conclusions

The experiences and needs of children with cancer and their families in all settings, whether a high-income or a developing country, need to be better understood.⁵⁶ Policy development needs evidence and experience. The table shows the policies proposed here and in the other three papers^{14–16} in this Series to focus our efforts to address the global needs of children with cancer. We need a broad and transdisciplinary approach to these issues that brings in expertise from outside the

For the UN Human Development Index website see <http://hdrstats.undp.org/en/indicators/default.html>

Search strategy and selection criteria

We searched databases containing mortality and incidence rates from WHO (the Global Burden of Disease) and the International Agency for Research on Cancer, and development indicators from the World Bank Group and UN Human Development Index databases. We searched PubMed and Scopus with the following strategy: "paediatric" OR "pediatric" OR "child" OR "children" AND "oncology" OR "cancer" OR "malignancy" OR "leukemia" OR "leukaemia" AND "international" OR "global" OR "developing" OR "low-income" OR "middle-income" AND "policy". The search included papers published from Jan 1, 1965, to Dec 31, 2012 in English. The results were supplemented with the authors' files and the papers referred to in the references retrieved. References are illustrative of the authors' major points, and are not exhaustive.

traditional childhood cancer community, and also leverages the solidarity that exists between all the communities involved in the care, research, and education agendas in childhood cancer. The delivery of improved global outcomes for children with cancer will need creative policy solutions to many issues, from fundamental biology to the delivery of new educational systems for sick children. Agreement, solidarity, and mutual help will be the most important means to fulfil these policy recommendations. In 2023, we should be able to look back and see real improvements in all the issues raised in this Series; although many goals are ambitious, none are out of reach.

Contributors

RS and KP-J framed the manuscript, and all authors then contributed equally.

Conflicts of interest

We declare that we have no conflicts of interest.

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References

- The World Bank. World Development Report 1980: poverty and human development; 1980. http://wdronline.worldbank.org/worldbank/a/c.html/world_development_report_1980/abstract/WB.0-1950-2834-1.abstract (accessed Dec 3, 2012).
- WHO. Globocan 2008: cancer incidence and mortality worldwide. <http://globocan.iarc.fr> (accessed Jan 2, 2013).
- Sullivan R. Putting public health back into the global cancer agenda. *Ann Oncol* 2012; **23**: 2995–96.
- Pui CH, Gajjar AJ, Kane JR, Qaddoumi IA, Pappo AS. Challenging issues in pediatric oncology. *Nat Rev Clin Oncol* 2011; **8**: 540–49.
- Chirdan LB, Bode-Thomas F, Chirdan OO. Childhood cancers: challenges and strategies for management in developing countries. *Afr J Paediatr Surg* 2009; **6**: 126–30.
- Hesseling PB, Molyneux E, Tshintseme F, et al. Treating Burkitt's lymphoma in Malawi, Cameroon, and Ghana. *Lancet Oncol* 2008; **9**: 512–13.
- Barr RD, Feeny D, Furlong W. Economic evaluation of treatments for cancer in childhood. *Eur J Cancer* 2004; **40**: 1335–45.
- Bhakta N, Martiniuk AL, Gupta S, Howard SC. The cost effectiveness of treating paediatric cancer in low-income and middle-income countries: a case-study approach using acute lymphocytic leukaemia in Brazil and Burkitt lymphoma in Malawi. *Arch Dis Child* (in press).
- Curado MP, Edwards B, Shin HR, et al. Cancer incidence in five Continents, Vol IX. IARC, Lyon; 2007.
- Parkin DM, Ferlay J, Hamdi-Cherif M, et al. Cancer in Africa: epidemiology and prevention. IARC: Lyon, 2003.
- Valsecchi MG, Steliarova-Foucher E. Cancer registration in developing countries: luxury or necessity? *Lancet Oncol* 2008; **9**: 159–67.
- Steliarova-Foucher E, Stiller C, Kaatsch P, et al. Geographical patterns and time trends of cancer incidence and survival among children and adolescents in Europe since the 1970s (the ACCISproject): an epidemiological study. *Lancet* 2004; **364**: 2097–105.
- Smith MA, Seibel NL, Altekruse SF, et al. Outcomes for children and adolescents with cancer: challenges for the twenty-first century. *J Clin Oncol* 2010; **28**: 2625–34.
- Pritchard-Jones K, Pieters R, Reaman GH, et al. Sustaining innovation and improvement in the treatment of childhood cancer: lessons from high-income countries. *Lancet Oncol* 2013; published online Feb 20. [http://dx.doi.org/10.1016/S1470-2045\(13\)70010-X](http://dx.doi.org/10.1016/S1470-2045(13)70010-X).
- Magrath I, Steliarova-Foucher E, Epelman S, et al. Paediatric cancer in low-income and middle-income countries. *Lancet Oncol* 2013; published online Feb 20. [http://dx.doi.org/10.1016/S1470-2045\(13\)70008-1](http://dx.doi.org/10.1016/S1470-2045(13)70008-1).
- Vassal G. New drugs for children and adolescents with cancer: the need for novel development pathways. *Lancet Oncol* 2013; published online Feb 20. [http://dx.doi.org/10.1016/S1470-2045\(13\)70013-5](http://dx.doi.org/10.1016/S1470-2045(13)70013-5).
- Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006; **355**: 1572–82.
- Gatta G, Zigon G, Capocaccia R, et al. Survival of European children and young adults with cancer diagnosed 1995–2002. *Eur J Cancer* 2009; **45**: 992–1005.
- Hays DM. Adult survivors of childhood cancer. Employment and insurance issues in different age groups. *Cancer* 1993; **71** (10 suppl): 3306–09.
- Houweling TA, Kunst AE. Socio-economic inequalities in childhood mortality in low- and middle-income countries: a review of the international evidence. *Br Med Bull* 2010; **93**: 7–26.
- Ribeiro RC, Steliarova-Foucher E, Magrath I, et al. Baseline status of paediatric oncology care in ten low-income or mid-income countries receiving My Child Matters support: a descriptive study. *Lancet Oncol* 2008; **9**: 721–29.
- Pritchard-Jones K. Clinical trials for children with cancer in Europe—still a long way from harmonisation: a report from SIOP Europe. *Eur J Cancer* 2008; **44**: 2106–11.
- Hoey R. The EU clinical trials directive: 3 years on. *Lancet* 2007; **369**: 1777–78.
- Eckhouse S, Sullivan R. A survey of public funding of cancer research in the European union. *PLoS Med*. 2006; **3**: e267.
- Gatta G, Capocaccia R, Coleman MP, Ries LA, Berrino F. Childhood cancer survival in Europe and the United States. *Cancer* 2002; **95**: 1767–72.
- Stefan DC, Stones DK. The South African paediatric tumour registry—25 years of activity. *S Afr Med J* 2012; **102**: 605–06.
- Usmani GN. Pediatric oncology in the third world. *Curr Opin Pediatr* 2001; **13**: 1–9.
- Aber JL, Bennett NG, Conley DC, Li J. The effects of poverty on child health and development. *Annu Rev Public Health* 1997; **18**: 463–83.
- Barton MB, Frommer M, Shafiq J. Role of radiotherapy in cancer control in low-income and middle-income countries. *Lancet Oncol* 2006; **7**: 584–95.
- Kellie SJ, Howard SC. Global child health priorities: what role for paediatric oncologists? *Eur J Cancer* 2008; **44**: 2388–96.
- Howard SC, Marinoni M, Castillo L, et al. Improving outcomes for children with cancer in low-income countries in Latin America: a report on the recent meetings of the Monza International School of Pediatric Hematology/Oncology (MISPHO)-Part I. *Pediatr Blood Cancer* 2007; **48**: 364–69.

- 32 Marmot M. The influence of income on health: views of an epidemiologist. *Health Aff (Millwood)* 2002; **21**: 31–46.
- 33 Wilkinson RG. Unhealthy societies. The afflictions of inequality. London: Routledge; 1997.
- 34 Mostert S, Sitaesmi MN, Gundy CM, Sutaryo, Veerman AJ. Influence of socioeconomic status on childhood acute lymphoblastic leukemia treatment in Indonesia. *Pediatrics* 2006; **118**: e1600–06.
- 35 Barro RJ, Lee JW. International measures of schooling years and schooling quality. *Am Econ Rev* 1996; **86**: 218–23.
- 36 Howard SC, Pedrosa M, Lins M, et al. Establishment of a pediatric oncology program and outcomes of childhood acute lymphoblastic leukemia in a resource-poor area. *JAMA* 2004; **291**: 2471–75.
- 37 Ahluwalia MS, Carter NG, Chenery HB. Growth and poverty in developing countries. *J Development Econ* 1979; **6**: 299–341.
- 38 O'Hare B, Venables J, Southall D. Child health in Africa: 2005 a year of hope? *Arch Dis Child* 2005; **90**: 776–81.
- 39 Starfield B, Shi L. Policy relevant determinants of health: an international perspective. *Health Policy* 2002; **60**: 201–18.
- 40 Adamson PC, Blaney SM. New approaches to drug development in pediatric oncology. *Cancer J* 2005; **11**: 324–30.
- 41 Pollack IF, Jakacki RI. Childhood brain tumors: epidemiology, current management and future directions. *Nat Rev Neurol* 2011; **7**: 495–506.
- 42 Moreno L, Chesler L, Hargrave D, Eccles SA, Pearson AD. Preclinical drug development for childhood cancer. *Expert Opin Drug Discov* 2011; **6**: 49–64.
- 43 Downing JR, Wilson RK, Zhang J, et al. The Pediatric Cancer Genome Project. *Nat Genet* 2012; **44**: 619–22.
- 44 Zhao L, Lee J, Mody R, Braun TM. The superiority of the time-to-event continual reassessment method to the rolling six design in pediatric oncology phase I trials. *Clin Trials* 2011; **8**: 361–69.
- 45 Brüggemann M, Schrauder A, Raff T, et al, for the European Working Group for Adult Acute Lymphoblastic Leukemia (EWALL); International Berlin-Frankfurt-Münster Study Group (I-BFM-SG). Standardized MRD quantification in European ALL trials: proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18–20 September 2008. *Leukemia* 2010; **24**: 521–35.
- 46 Hudson MM, Neglia JP, Woods WG, et al. Lessons from the past: opportunities to improve childhood cancer survivor care through outcomes investigations of historical therapeutic approaches for pediatric hematological malignancies. *Pediatr Blood Cancer* 2012; **58**: 334–43.
- 47 Franco VI, Henkel JM, Miller TL, Lipshultz SE. Cardiovascular effects in childhood cancer survivors treated with anthracyclines. *Cardiol Res Pract* 2011; **2011**: 1–13.
- 48 Wells EM, Nageswara Rao AA, Scafidi J, Packer RJ. Neurotoxicity of biologically targeted agents in pediatric cancer trials. *Pediatr Neurol* 2012; **46**: 212–21.
- 49 Zwaan CM, Kearns P, Caron H, et al. The role of the 'innovative therapies for children with cancer' (ITCC) European consortium. *Cancer Treat Rev* 2010; **36**: 328–34.
- 50 Pritchard-Jones K, Lewison G, Camporesi S, et al. The state of research into children with cancer across Europe: new policies for a new decade. *eCancerMedicalScience* 2011; **5**: 210.
- 51 Pritchard-Jones K, Dixon-Woods M, Naafs-Wilstra M, Valsecchi MG. Improving recruitment to clinical trials for cancer in childhood. *Lancet Oncol* 2008; **9**: 392–99.
- 52 Hearn J, Sullivan R. The impact of the 'Clinical Trials' directive on the cost and conduct of non-commercial cancer trials in the UK. *Eur J Cancer* 2007; **43**: 8–13.
- 53 Saracci R, Olsen J, Seniori-Costantini A, West R. Epidemiology and the planned new Data Protection Directive of the European Union: a symposium report. *Public Health* 2012; **126**: 253–55.
- 54 Thorat C, Xu K, Freeman SN, et al. What the Orphan Drug Act has done lately for children with rare diseases: a 10-year analysis. *Pediatrics* 2012; **129**: 516–21.
- 55 Vassal G. Will children with cancer benefit from the new European Paediatric Medicines Regulation? *Eur J Cancer* 2009; **45**: 1535–46.
- 56 McGrath P, Phillips E. "It is very hard": treatment for childhood lymphoma from the parents' perspective. *Issues Compr Pediatr Nurs* 2008; **31**: 37–54.
- 57 Jolanta Kwasniewska's Foundation, European Society of Paediatric Oncology. European standards of care for children with cancer. [www.siope.eu/binarydata.aspx?type=doc/European_Standards_final_2011\(1\).pdf](http://www.siope.eu/binarydata.aspx?type=doc/European_Standards_final_2011(1).pdf) (accessed Dec 12, 2012).