The strategic plan for paediatric cancer treatment and clinical research development in Belgium

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SUMMARY

Childhood cancer can be cured in a good proportion of patients, but outcome rates are still unsatisfactory for specific cancer types and for resistant or relapsed disease. Collaborative clinical research is required for further outcome improvement as well as easier access for children to innovative treatments. Moreover, clinical care standards and clinical research infrastructure in Belgium should be optimised and structurally financed to reach the level proposed by international professional and scientific organisations. In this strategic plan, obstacles are analysed, and solutions for improved childhood cancer care and clinical research in Belgium are proposed.

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INTRODUCTION

Since the first successful treatments of paediatric cancer patients, considerable improvement in patient survival rates has been achieved. Currently, 80-90% of patients survive after five years, due to international collaborative clinical research. The area of paediatric haematology-oncology (PHO) is small in terms of patient numbers, but extremely diverse as it covers at least 60 different types of cancer in a population ranging from new-borns to teenagers and young adults. Today, as our biological understanding of cancer has improved, and biomarker analysis is becoming available, the field is even more heterogeneous, underscoring the importance of multicentre and international scientific collaboration. However, continued improvement in paediatric cure rates has stagnated in the last fifteen years while very few innovative cancer treatment options have become routinely available for children and adolescents, in contrast to the situation for adults. In adult cancer, lower survival rates justify innovative treatments for a larger population, whereas in children innovative treatments are so far mostly justified

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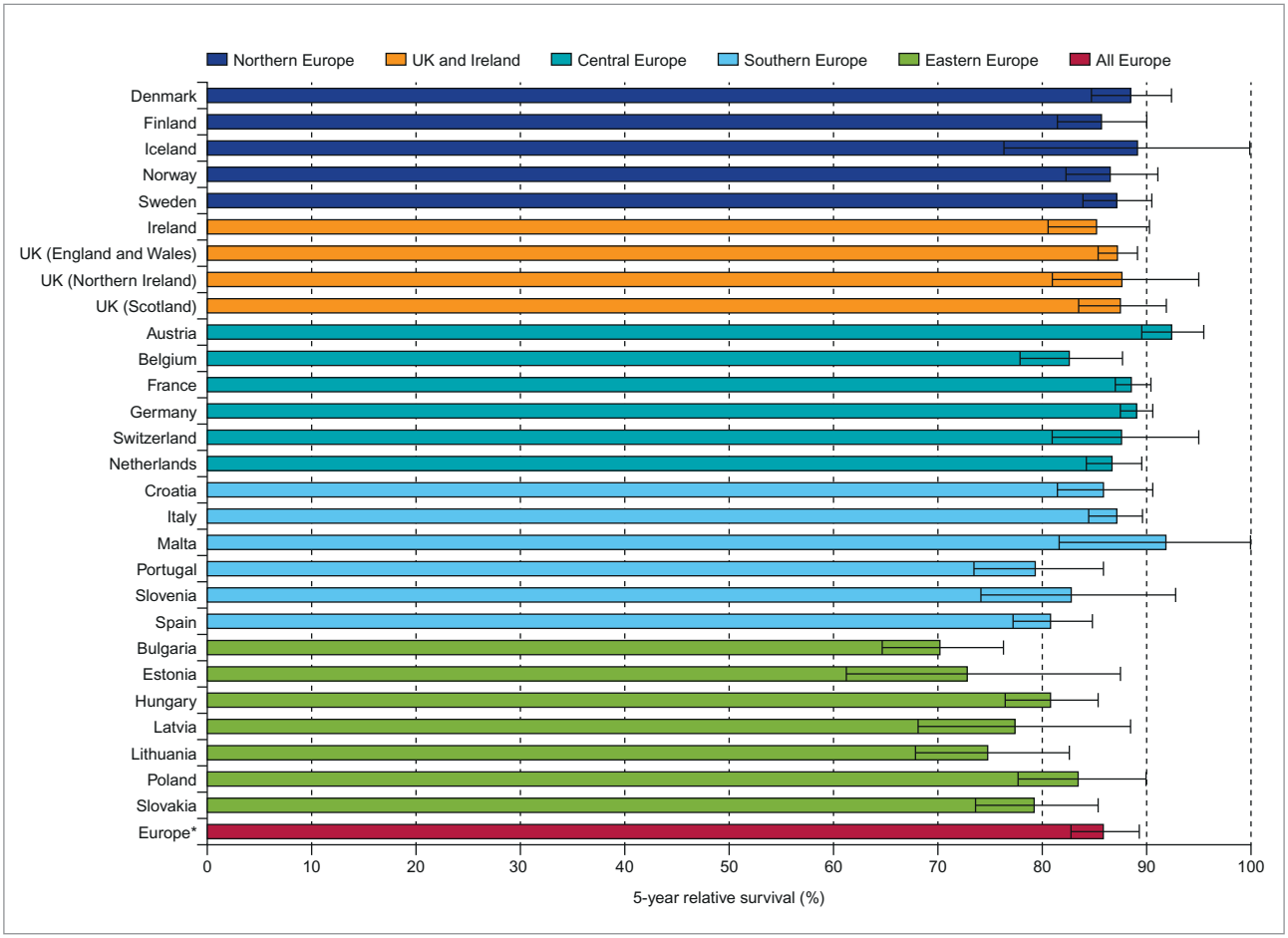

FIGURE 1. Five-year survival for acute lymphoid leukaemia diagnosed in 2000-2007 in European children by country.[2]

only for exceptional cases of treatment resistance or relapse. Nevertheless, the long-term effects of paediatric cancer can be more devastating than in adults, since it occurs early in life and the late effects from disease and treatment continue to develop over several decades, further justifying the continued need to improve treatments and outcomes.

The practice of paediatric oncology is unique as optimal treatment ideally includes participation of patients in clinical trials, meaning that standard of care is, in most instances, treatment in the framework of a(n) (inter)national academic clinical trial. This is an unusual situation, differing from the situation of adult oncology. As paediatric cancer is inherently rare, treatment of a maximal number of patients in clinical trials is required to include sufficient numbers of patients to gain meaningful results regarding biological insights and therapeutic and prognostic improvements. However, these trials are not funded by the pharmaceutical industry and often rely entirely on charity funding from the participating countries. Most innovative drugs and treatments in paediatric oncology have been brought forward by investigator-driven clinical trial groups. Worldwide, several professional organisations were founded, some national, some international (such as the International Society for Paediatric Oncology [SIOP]). The European branch of SIOP (SIOPe) assembles established national PHO societies such as the Belgian Society for Paediatric Haematology and Oncology (BSPHO) and consists of several disease-specific working groups that are the driving force behind numerous European multicentre trials.

Because of the low absolute incidence of childhood cancer, Belgian centres participate in international clinical trials, in the framework of these scientific groups. Considerable effort has been made by Belgian centres to facilitate access to clinical trials and to run these trials conform the current regulations. The Belgian government has supported this attitude by providing support in the Belgian Cancer Plan. This cancer plan, implemented in 2010 and described in a Royal Decree on April 2nd, 2014, in the Belgian Statute Book (Staatsblad/Moniteur Belge), defines the minimal staffing standards for specialised and satellite PHO sites in Belgium. Nevertheless, even if the cancer plan has allowed for significant progress in the organisation and staffing of paediatric oncology teams in Belgium, requirements and developments on European level have moved further. According to the publication of the SIOPe Strategic Plan, the

actual Belgian outcome results for acute lymphoblastic leukaemia (ALL) in children, while being acceptable, seem to compare somewhat unfavourably with other Western European countries. These results have to be interpreted with caution, as it is not clear if survival registration in other European countries is done in the same rigorous way as in the Belgian Cancer Registry (*Figure 1*).[1-3] International comparison data, recently analysed in the Concord-3 study, show excellent outcomes for ALL and lymphoma in Belgium but give the impression of some stagnation in further prognosis improvement as far as brain tumour outcomes are concerned.[4]

As Belgium is a small country, the organisation of optimal access to innovative treatments and early phase clinical trials for Belgian paediatric oncology patients faces significant hurdles and is generally more limited than in large European countries as Germany, France and the UK. We describe the reasons behind this situation by analysing the current state of paediatric oncology care in Belgium, the differences with other European countries and the current requirements. We provide proposals to align Belgian paediatric oncology care and clinical research with the European standards.

EUROPEAN STANDARDS OF CARE FOR CHILDREN WITH CANCER AND COMPARISON WITH THE CURRENT SITUATION IN BELGIUM

In 2009, SIOPe published a reference document online entitled 'European Standards of Care for Children with Cancer', which led to the publication by Kowalczyk *et al.* in 2014.[5] It describes the minimal requirements needed to provide optimal care to paediatric oncology patients, in terms of infrastructure as well as common work practices. Centres participating in clinical trials should adhere to these requirements in order to obtain comparable results and common outcomes.

For medical staff, the SIOPe document describes a requirement of two full-time paediatric oncologists per 30 new paediatric oncology diagnoses per year, with a higher ratio if the centre has a stem cell transplant activity. Since the implementation of the Belgian Cancer Plan in 2010, Belgian centres receive funding to fulfil most requirements concerning nursing and paramedical staff, although this envelope is fixed and does not follow indexation or inflation. The medical standards described in the Belgian Cancer Plan require two staff members for a centre with less than 50 diagnoses per year; four physicians for centres with more than 50 diagnoses per year plus two extra physicians in transplant centres. This is in accordance with the minimal medical staffing requirements across Europe as described by SIOPe. The Cancer Plan, however, does not provide criteria for centres treating more than 60 new patients per year (as those centres would require more than four physicians according to SIOPe requirements), does not consider the care for refractory or (multiple) relapsing patients nor for innovative treatments and does not finance physician's salaries. Despite the recent recognition of PHO as a subspecialty of paediatrics, with adjusted INAMI/RIZIV nomenclature, hospitals are still struggling to financially justify this absolute minimal number of paediatric oncologists. In addition, the minimal European standards described compare unfavourably with what has been studied and adopted as staffing requirements in Canada, where medical staff requirements correspond to approximately twice the number of physicians working in our Belgian centres.[6]

The SIOPe standards further describe the need for government or insurance companies to fully reimburse the costs of the treatment according to the recommended therapeutic programme, including standard of care drugs used 'off-label'. In Belgium, registration for a specific PHO indication or paediatric age group is often lacking for chemotherapeutic and supportive care drugs commonly used as standard of care, leading to routine off-label use of these drugs in children. As in Belgium, reimbursement is often based on registration criteria, considerable financial difficulties can arise.

European Reference Networks (ERNs) are the European Union's initiative that will make national health systems cooperate in the interest of patients. The newly created ERN on Paediatric Cancer (ERN PaedCan) and its subdivisions contain several large, Belgian treatment centres. It aims at reducing inequalities in childhood cancer survival by providing high-quality, accessible and cost-effective cross-border healthcare to European children and adolescents with cancer. PaedCan will also implement eHealth technologies and improve interoperability across different institutions. Especially for rare cancers, this initiative will result in the centralisation of patient care and hence expertise. This is further enhanced by the PARTNER initiative, which is a three-year long project part of PaedCan, that aims to create a Paediatric Rare Tumour European Registry dedicated to children and adolescents with very rare tumours, linking existing national registries.

Since 2010, Action 12 of the Cancer Plan provides 191,240 euros per year for 'the stimulation of research in PHO and for networking between centres'. This was the incentive for the foundation of the National Coordination Cell Clinical Trials in 2011. The goal of the coordination cell is the advancement of clinical research in paediatric oncology in Belgium through support of administrative burden of clinical trials, better registration of childhood cancer in Belgium, improved networking between centres and coordination of clinical research efforts between centres.

The coordination cell is led by a coordinating physician (0.1 FTE) and funds a full-time collaborator at the Belgian Cancer Registry who specifically works on paediatric cancer registration. The principal activities of the coordination cell consist of administrative and logistic support of clinical trials in the Belgian centres (Clinical Trial Cell), with 1.5 FTE collaborators based in three different PHO centres. This support is currently limited to academic clinical trials with no or very limited central funding, executed in the frame of international collaborations. More recently, data monitoring, grant applications and centralising severe adverse events have been added to the task list of the Clinical Trial Cell. The first studies prepared and supported by the Clinical Trial Cell opened and included patients in 2012. More than twenty trials opened with the support of the coordination cell so far.

Since the launch of the Clinical Trial Cell, the opening of an academic late phase clinical trial has become more feasible for the PHO centres. Nevertheless, there is still no structural budget to cover the costs of academic clinical research. This concerns on the one hand issues of reimbursement of off-label, yet well-established standard of care therapies and on the other hand costs of no-fault insurance, pharmacy fees, data collection, pathology/imaging review – which serves as quality control and allows clinical benchmarking in the European context – biobanking, etc. All clinical trials, including academic late phase clinical trials, require rigorous data monitoring.[7] Consequently, implementing these late phase clinical trials, which provide access to best current care to patients, in the Belgian PHO sites, requires additional staff and financing.

All Belgian paediatric oncology centres employ at least one clinical trial manager, usually funded by charity sources. These local trial managers are responsible for support of the local investigators, the local trial initiation (introduction ethical committee, budget, contracts, etc.) and implementation, data management, safety reporting, etc.

In comparison, 'Stichting Kinderoncologie Nederland' (SKION), which is the Dutch counterpart of the coordination cell and which is funded by the health insurance system in the Netherlands, employs 30 clinical trial managers located at the centres and approximately 40 people based at the central office: 13 in the clinical trial centre, 10 in administration, 13 in the laboratory, 1 statistician, 1 IT manager and 3 managers involved in quality of data and the late effects project.[8] SKION's annual budget is around 4,000,000 euros/year.

EARLY-PHASE CLINICAL TRIALS IN PAEDIATRIC ONCOLOGY IN BELGIUM

Children with specific subtypes of cancer or with (multiple) relapse(s) or refractory disease may be eligible for (industry-sponsored or academic) early-phase clinical trials (ECTs), typically triggered by a paediatric investigation plan under the EU Paediatric Regulation.[7,9] Nevertheless, still very few therapeutic innovations in cancer are actually reaching children because of the possibility to obtain waivers for paediatric drug development in the context of the Paediatric Regulation, and because of delays while waiting for adult results, which are not relevant for paediatric cancer, and the inappropriate translation of the adult situation to children.[10]

Today, participation in an innovative treatment trial is relevant for a number of paediatric cancer patients although rarely being life-saving, since this is usually not the aim of such early-phase pharmacokinetic and safety trials. Currently, only a small fraction of those early-phase industry-sponsored trials are recruiting in Belgium. To enrol or explore possibilities for enrolment in such trials, children with advanced cancer may have to travel abroad. The financial burden for the family can be substantial, since the study-sponsor only covers study-related costs and not the costs for supportive care, travel and interim housing. Moreover, the emotional and social burden for these families can be unacceptable. Administrative and insurance hurdles are often substantial. Nevertheless, some first line late-phase clinical trials contain a treatment window in which an innovative drug is used and where the same standards and regulations as for an early-phase trial are applicable. This means that the implementation of these treatment opportunities in Belgium is imperative to ensure optimal care. Altogether, current regulations, rising standards and growing demands of clinical trial operations increasingly require resources and infrastructure that are currently not readily available in Belgium.

The Paediatric Oncology Department of the Ghent University Hospital, as Innovative Therapies for Children with Cancer (ITCC; see below) institution, conducts ECTs, mainly in the area of paediatric malignant haematology, while other paediatric/haematology departments of large centres are also conducting early-phase trials in the framework of early-phase facilities in their hospitals, aiming to increase the capacity for ECT access for Belgian patients within the country. Nevertheless, many Belgian paediatric oncology patients in advanced, relapsed or refractory disease situations for which no standard treatment is available, still have no access to innovative treatments in the frame of an ECT.

SITUATION IN OTHER EUROPEAN COUNTRIES

Medicine reimbursement and health care financing systems vary widely across Europe. In our neighbouring Western European countries, there is, through a combination of public and private research and health care funding sources, sub-

stantial structural funding to support paediatric oncology clinical research infrastructure (such as the 'programme hospitalier de recherche clinique' [PHRC] in France, National Health Service [NHS] in the UK, etc.). All patients benefit from such infrastructure, from those receiving initial standard treatment to those with advanced disease enrolling in early-phase industry-sponsored trials, and it is an asset to attract the interest of pharmaceutical companies selecting sites for their European studies.

The Innovative Therapies for Children with Cancer consortium was created in 2003 as a non- profit organisation under the French Law. It gathers 56 European paediatric/oncology departments with expertise in conducting ECTs for children and 22 European research laboratories. The aim is to coordinate the development of novel therapies for children with cancer, in cooperation with regulatory bodies, pharmaceutical enterprises, parents and patients. Other ECTs are being conducted in sites with early-phase trial expertise outside the ITCC network through direct interaction between the pharmaceutical industry and the sites.

PROPOSAL

We propose to expand and professionalise the existing support structure for late-phase paediatric oncology clinical trials in Belgium (BSPHO Coordination Cell Clinical Trials), to align our capacity and opportunities for patients with what is available in our neighbouring countries. We propose the establishment of a cost-effective, state-of-the-art, integrated paediatric oncology clinical trial infrastructure to support innovation in this area with substantial medical need in Belgium.

We identified the need to engage additional clinical trial managers, an accountant for the overview of grants and financial management, an administrative support professional, a legal advisor, an IT specialist and clinical trial monitors. Local clinical trial managers should be funded at a ratio of at least 1 per 20 new diagnoses per year, meaning ranging from 2 to 6 per centre. Moreover, a central funding agency that can review the scientific merits of a certain trial and can fund all non-structural costs related to a specific trial (such as central review, transport and molecular analysis of samples and other costs) could streamline the funding applications. Currently, trials can only be funded for a short period of time, sometimes even separate funding application submissions are needed for the different Belgian regions. Such a centralised funding agency would enhance the cost-efficiency of the personnel involved in the preparation and support of the clinical trials significantly. Several European countries, such as France and the UK are organised in this way (PHRC, UK Children's Cancer Study Group).

Considering the development of a more extensive ECT activity (industry and academic) in Belgium, the Belgian centres have agreed in a first step to organise teleconferences for ECT. These teleconferences take place within one week after an inquiry to explore the feasibility of an ECT, and participants from all centres are invited. During these teleconferences, the participants discuss the trial, feasibility and utility in Belgium, explore competing trials and aspire to conclude on one or more centres that will accept the trial and the commitment of the other centres to refer their eligible patients. In this way, we aim to prioritise trials, based on their scientific merit and potential benefit for patients and centralise the effort and expertise needed for conducting these trials.

Several centres are developing ECT activities, thus enhancing ECT capacity for children with cancer, without undue competition between the centres following the commitments made in the teleconference as described. The collaboration between these centres and central support from the existing coordination cell is being organised. Potential eligible patients for early- or late-phase trials will be discussed in weekly national teleconferences, provided sufficient support can be secured to organise these meetings. For these centres, a dedicated local physician responsible for clinical trials should be funded, for the supervision of early- and/or late-phase clinical trial activities. For each centre that develops ECT activities, at least one paediatric clinical trial nurse and a pharmacist should be funded. Ideally, one clinical research coordinator, one data manager and a part-time administrator/accountant should also be available per centre. Beside the development of this clinical trial infrastructure, drugs that are standard of care in these trials should be reimbursed. It is no longer acceptable that standard of care treatment for paediatric oncology patients is funded by charity money, as is still too often the case today. Furthermore, clinical staffing levels required to secure this level of care and development need to be structurally funded as it is part of what is considered standard of care in the international paediatric oncology community. These measures would allow the Belgian centres to optimise their quality of care, improve outcome levels and align clinical research activities in late-phase clinical trials with European standards. It would create optimal access to early-phase trials with new compounds for all types of relapsed or refractory paediatric cancer and improve the infrastructure needed to provide all of the above.

CONCLUSION

Despite the recent improvements in the organisation and execution of late-phase multicentre clinical trials in paediatric oncology in Belgium, resources are limited compared to oth-

KEY MESSAGES FOR CLINICAL PRACTICE

1. As paediatric cancer is inherently rare, standard of care treatment includes inclusion in a clinical trial when possible.
2. Organisation of clinical trial infrastructure is therefore crucial to ensure optimal care for patients.
3. Resources provided for this endeavour are limited in Belgium.
4. Expansion of the medical, paramedical and scientific staff, as well as reimbursement of off-label drugs used in the standard of care setting is urgently needed to ensure adhesion to European standards.

er European countries. Current medical and supportive staff levels, while committed to provide the required high standards of clinical care as well as early- and late-phase clinical trial opportunities for patients, are insufficient to ensure continued adhesion to developments on the international level. The Belgian National Cancer Plan has permitted the alignment of paramedical staffing of paediatric oncology centres to European Standards, but medical staffing and clinical research support is currently still suboptimal, which is of great concern to all stakeholders involved. With minimal means, the BSPHO has created a coordination cell for clinical trials in paediatric oncology in Belgium, which is functioning very well and has significantly improved the preparation of late-phase clinical trials. However, funding for conducting clinical trials is difficult to obtain, while costs are increasing due to increasing regulatory requirements. Nevertheless, this structure is solid and can be expanded to answer to current limitations in clinical trial execution, ECT availability and childhood cancer outcomes, if given adequate financial means. Continued and additional efforts are required to achieve the level of care and innovation comparable to our neighbouring countries. Structural funding for standard of care drugs, used off-label in paediatrics, should be provided.

REFERENCES

1. Vassal G, Schrappe M, Pritchard-Jones K, et al. The SIOPe Strategic Plan. A European cancer plan for children and adolescents. J Cancer Policy. 2016;8(6):17-32.
2. Gatta G, Botta L, Rossi S, et al. Childhood cancer survival in Europe 1999-2007: results of EUROCARE-5 – A population-based study. Lancet Oncol. 2014;15(1):35-47.
3. Belgian Cancer Registry. Cancer in Children and Adolescents. 2013. Available from http://www.kankerregister.org/media/docs/publications/CancerInc-Bel2010-ChildrenAdolescents.pdf.
4. Allemani C, Matsuda T, Di Carlo V, et al. CONCORD Working group. Global surveillance of trends in cancer survival 2000-14 (CONCORD-3): analysis of individual records for 37 513 025 patients diagnosed with one of 18 cancers from 322 population-based registries in 71 countries. Lancet. 2018;391(10125):1023-75.
5. Kowalczyk J, Samardakiewicz M, Fitzgerald E, et al. Towards reducing inequalities: European Standards of Care for Children with Cancer. Eur J Cancer. 2014;50(3):481-85.
6. Halton J, Hand J, Byron P, et al. Establishing physician to patient ratios and predicting workforce needs for Canadian pediatric hematology-oncology programs. Pediatr Blood Cancer. 2013;60(4):564-69.
7. The European parliament and the council of the European Union. EU Clinical trial Directive, Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 , Official Journal L 378. 2006. Available from https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/reg_2006_1901/reg_2006_1901_en.pdf.
8. SKION. Jaarverslag SKION 2015. Available from http://metacultura.nl/SKION2015/.
9. European Commission. State of Paediatric Medicines in the EU. 10 years of the EU Paediatric Regulation. 2017. Available from https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/2017_childrensmedicines_report_en.pdf.
10. Vassal G, Rousseau R, Blanc P, et al. Creating a unique, multi-stakeholder Paediatric Oncology Platform to improve drug development for children and adolescents with cancer. Eur J Cancer. 2015;51(2):218-24.