Indian Pediatric Oncology Group (InPOG) – Collaborative research in India comes of age

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A B S T R A C T

Treatment of children with cancer on clinical trials, often in the context of national and international co-operative groups, is one of the cornerstones of pediatric oncology treatment and has been shown to improve outcomes of children with cancer. While enrolling children with cancer in prospective multi-centre trials has become the norm in high-income countries, it has remained an exception in low and middle-income countries until recently. In this article, we briefly review the global landscape of pediatric oncology co-operative groups and then discuss the Indian scenario including more recent developments of the formation and galvanization of the Indian Pediatric Oncology Group (InPOG). The mission of InPOG is to improve the outcomes of children with cancer in India by collaborative research. A roadmap for the development and conduct of an InPOG study has been created and 21 disease-specific subcommittees have been formed. Multi-centre studies on Hodgkin lymphoma and acute lymphoblastic leukemia are currently recruiting and several others are under development.

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Management of children with cancer offers one of the most striking examples of progress in modern medicine. In the 1950s, less than 10 percent of children with cancer were cured. Today, nearly 80 percent will survive the disease [1,2]. Many factors can be attributed for this progress: multimodality treatment, combination chemotherapy, improved drugs, risk stratification and supportive care. Underpinning all these has been the early incorporation of research and multi-centre clinical trials often in the context of national (and increasingly international) co-operative groups [3–6]. Such an approach, which is one of the cornerstones of pediatric oncology treatment, has been shown to improve outcomes of children with cancer [6–8] and is the accepted form of delivering treatment in the 21st century [4,9].

Collaboration in treating children with cancer is a necessity as it is a relatively rare disease. This allows for pooling of data, comparison of results, and ultimately, improved outcomes. By systematically testing novel agents and treatment combinations/schedules in comparison with alternate protocols (often in a randomized fashion), the studies from cooperative groups have helped determine the most effective agent or treatment strategy which is then incorporated into successive clinical trials. Moreover, the multi-disciplinary nature of these groups brings together professionals from diverse backgrounds and different expertise, hence allowing for exchange of ideas, discussion and innovation.

In this article, we briefly review the global landscape of pediatric oncology co-operative groups and then discuss the Indian scenario including more recent developments of the formation and galvanization of the Indian Pediatric Oncology Group (InPOG).

1. Evolution of global pediatric oncology co-operative groups and collaborative research

The origins of pediatric oncology co-operative groups can be traced back to 1955 with the formation of the Cancer and Leukemia Group B Cooperative Group as well as the Acute Leukemia Chemotherapy Cooperative Study Group A (forerunner of the Children’s Cancer Group), both in USA [4,10]. Published in 1960, the comparison of 6-mercaptopurine versus the combination of 6-mercaptopurine and azaserine in the treatment of acute leukemia in children, is regarded as the first multi-centre co-operative clinical trial in childhood cancer [11]. Over the next two decades, other...
co-operative groups including Southwest Cancer Chemotherapy Study Group (forerunner of the Pediatric Oncology Group), National Wilms Tumor Study Group, and Intergroup Rhabdomyosarcoma Study Group were established in USA [4,10]. All these groups conducted landmark multi-centre prospective clinical trials allowing for significant advancements in the outlook of children with cancer [10]. In the year 2000, they all merged into a single cooperative group - the Children’s Oncology Group (COG) in order to combine efforts, accelerate progress and share resources. With over 5000 members from 240 pediatric cancer centers located in seven countries (Australia, Canada, Mexico, Netherlands, New Zealand, Switzerland, USA) more children with cancer have been treated by COG than by any other group [4,10]. Recently COG has brought out a series of publications which serve as a five year blueprint for research within the organization [12].

Emulating the practice from USA, similar co-operative groups were formed mainly in Europe and some other high-income countries (HIC) like Japan. The earliest and most notable among these groups were the United Kingdom Children’s Cancer Study Group (forerunner of the Children’s Cancer and Leukaemia Group) and the various working groups in Germany for leukemias (including BFM which represented centres in Berlin, Frankfurt and Munster) and solid tumours which fused under the Society for Paediatric Oncology/Haematology representing Germany and Austria [13,14]. 70–90% of children with cancer in these countries are enrolled on clinical trials [13,14]. Despite formation of national co-operative groups, the rarity of several childhood cancers like medulloblastomas [15], Hodgkin lymphomas [16], neuroblastomas [17], Wilms tumour [18], liver tumours [19] and sarcomas [20,21], has necessitated collaborations in Europe (several under the umbrella of International Society of Pediatric Oncology) with clinical trials which have transcended geographical boundaries. For clinical trials on certain childhood cancers like osteosarcoma and B-cell non-Hodgkin lymphoma there have even been transatlantic collaborations between COG and European institutions [22,23].

While enrolling children with cancer in prospective multi-centre trials has become the norm in HIC, it has remained an exception in low and middle-income countries (LMIC) until recently. The clinical trials conducted by the Brazilian Pediatric Oncology Group is an example of such exception, although only a minority of children with cancer in Brazil get enrolled on their clinical trials [24]. In such a backdrop at the start of the 21st century, multi-centre, multinational collaborative efforts have sprung in LMIC with Central America and Africa leading the way. The Asociación de Hemato-Oncología Pediátrica de Centro América (established 1998) is a consortium of seven Central American countries (Guatemala, Honduras, El Salvador, Nicaragua, Costa Rica, Panama, Dominican Republic) supported by several institutions in North America and Europe [25]. An area of focus has been the development of shared clinical protocols which now exist for most childhood cancers [25], and results based on the prospective use of some of these have been published [26–28]. Another example has been the Franco-African Childhood Cancer Group, established in 2000, which currently includes 15 countries in francophone Africa supported by institutions in France [29]. They have published prospective multi-centre studies on Burkitt lymphoma and Wilms tumour [30–32] with collaborative work ongoing on acute lymphoblastic leukemia, Hodgkin lymphoma and retinoblastoma [29]. The latest entry into these path-breaking collaborations in LMIC has been the Collaborative Wilms Tumour Africa Project, an initiative by colleagues from 8 institutions in 5 countries in Sub-Saharan Africa (Cameroon, Ethiopia, Ghana, Malawi, Uganda) which are among the poorest in the world [33]. Another exciting development has been the recent collaboration in the field of pediatric and adolescent germ cell tumors between several institutes in HIC and institutes from Brazil, Egypt and India [34].

2. The history of collaborative efforts in pediatric oncology in India

Dedicated pediatric oncology units first started to appear in India in the early 1980s and were confined to major metropolitan centres. The Pediatric Hematology and Oncology (PHO) chapter of Indian Academy of Pediatrics (IAP) was established in 1987 [35]. With a focus on building capacity and quality by training, it embarked upon organizing conferences and workshops, along with initiating fellowship programs including the pediatric hematology oncology fellowship by the National Board of Exams. A key initiative was the Indian National Training Project in Practical Pediatric Oncology organized to train pediatricians, pediatric surgeons, and postgraduates in the early recognition of childhood malignancies and to prepare them for ‘shared’ care of these children [35]. There was no collaborative research or clinical trials conducted during this period under the aegis of PHO IAP.

The earliest report of collaboration in the field of pediatric oncology in India was that between Cancer Institute, Chennai and the National Cancer Institute, USA in the early 1980s. Adopting a more intense protocol (MCP841) than that being used at the time, led to an improvement in the event free survival of acute lymphoblastic leukemia from 20% to 40% [36]. This treatment strategy was then adopted by Tata Memorial Hospital, Mumbai in 1986 and All India Institute of Medical Sciences, New Delhi in 1992 [37]. With this common protocol, event free survival rates of 40–60% were achieved and result of this landmark collaboration, remains the only published prospective multi-centre intervention study related to childhood cancer from India till date [37].

As we entered the 21st century, the scientific output of the Indian pediatric oncology community began to surge in the form of scientific presentations and publications [38,39]. However, these were of relatively low scientific quality and there was a glaring absence of multicenter studies [38,39]. Around the same time, but distinct from these “scientific” efforts, philanthropic initiatives partnering with treatment centres became increasingly prevalent in India. These not only supported the medical treatment, but also provided more holistic support with nutritionists, nurses, social workers, logistics, data managers, etc. The most recognizable among these were JivDaya Foundation and Cancids ... Kidscan, both of whom had a national footprint [40]. Although even here, collaborative research or clinical trials was not an area of focus, their efforts brought individuals from across India together and the additional resources like databases, data managers, nurses, etc. made the start of collaborative research more viable.

3. Indian Pediatric Oncology Group (InPOG)

The need to establish a national cooperative group in order to develop prospective multi-centre clinical trials in India became increasingly apparent. Such a strategy was critical to understand the biological differences in the disease, to assess responses to treatment and ultimately to improve childhood cancer survival in India. With this goal in mind, some members of the PHO IAP led by Dr Bharat Agarwal, Dr Purna Kurkure and Dr Anupam Sachdeva formed InPOG in 2008 [41]. The mission of InPOG is to improve the outcomes of children with cancer in India by collaborative research. The focus during the early years of InPOG was to put the systems in place to allow the running of such a group.
By 2014, InPOG was ready to take the next step in fulfilling its mission. All members of PHO IAP who had an interest in research were invited to join InPOG and asked to specify their areas of interest. This information was used to create 21 subcommittees and populate the members of each along with nomination of the chair (Table 1). The role of each InPOG subcommittee is to:

- Develop broad goals and specific objectives for the respective subcommittee
- Initiate and promote multicenter clinical trials and other research in their field
- Identify a panel of Indian and international reviewers relevant to their field

A roadmap for the development and conduct of an InPOG study has been created (Fig. 1). This defines the roles of the primary investigator, the reviewers, the InPOG subcommittees and the InPOG executive along with the desired timelines to execute some of the actions on the roadmap. A key recommendation is that a minimum of 5 centers have to participate in a collaborative study to be eligible to be considered as an InPOG study. The current portfolio of InPOG studies is displayed in Table 2. This includes two currently recruiting studies on Hodgkin lymphoma and acute lymphoblastic leukemia as well as several others, which have been granted provisional InPOG registration and are under development.

Currently there are 109 members of InPOG from 55 institutes in India of which the majority (70%) are pediatric hematologists/oncologists. These members work in hospitals in the private sector (48%), the public sector (43%) and others (9%), and half of them work in centres where >100 newly diagnosed childhood cancer patients are treated every year. 48% of InPOG members have more than 10 years experience working with children with cancer and 57% have more than 10 peer-reviewed publications.

New collaborative endeavors like InPOG bring with them their own challenges, particularly in the early formative years. This is especially relevant in the Indian context where there is significant heterogeneity among treating centres with regard to annual patient caseload as well as the financial model of service delivery. Moreover, there have been no previous standards set or guidelines issued as to what constitutes a treatment centre, neither is there any regulation to enforce this. While this is desirable and would improve the quality of treatment (and research), undertaking any activities in this direction are outside the scope of InPOG. Other challenges relate to administrative, regulatory and procedural issues. These include, acquiring funds, developing standard operating procedures, understanding regulatory barriers, developing clinical trial management systems and promoting research governance. Members of the InPOG executive are tasked with addressing these and steady progress is being made.

Further issues include lack of trained manpower, in this case, clinicians with training and experience in multi-centre clinical trials as well as an absence of a pool of statisticians and other research staff which would form the bedrock of developing these clinical trials and taking them to fruition. An important development has been the increasing number of trained pediatric oncologists from Indian institutes as well as those emigrating from outside India who now form the critical human resource needed for such a collaborative group to succeed and harnessing

Table 1
InPOG disease subcommittees and chairs.

<table>
<thead>
<tr>
<th>Subcommittee</th>
<th>Chair</th>
<th>Affiliations</th>
<th>Contact email address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute lymphoblastic leukemia</td>
<td>Prof Vaskar Saha</td>
<td>Tata Medical Center, Kolkata</td>
<td><a href="mailto:vaskar.saha@tmckolkata.com">vaskar.saha@tmckolkata.com</a></td>
</tr>
<tr>
<td>Acute myeloid leukemia</td>
<td>Dr Sameer Bakhshi</td>
<td>Dr. BRA Institute Rotary Cancer</td>
<td><a href="mailto:sambakh@hotmail.com">sambakh@hotmail.com</a></td>
</tr>
<tr>
<td>Hodgkin lymphoma</td>
<td>Dr Jagdish Chandra</td>
<td>Lady Hardinge medical College, Kalawati Saran Children's Hospital, New Delhi</td>
<td><a href="mailto:jchandra55@gmail.com">jchandra55@gmail.com</a></td>
</tr>
<tr>
<td>Non-hodgkin lymphoma</td>
<td>Dr Amita Trehan</td>
<td>Postgraduate Institute of Medical Education &amp; Research, Chandigarh</td>
<td><a href="mailto:trehanamita@hotmail.com">trehanamita@hotmail.com</a></td>
</tr>
<tr>
<td>Chronic myeloproliferative disorders</td>
<td>Dr Deepak Bansal</td>
<td>Postgraduate Institute of Medical Education &amp; Research, Chandigarh</td>
<td><a href="mailto:deepakbansalr@gmail.com">deepakbansalr@gmail.com</a></td>
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<tr>
<td>Central nervous system tumours</td>
<td>Dr Girish Chinnaswamy</td>
<td>Tata Memorial Hospital, Mumbai</td>
<td><a href="mailto:girish.c.tmh@gmail.com">girish.c.tmh@gmail.com</a></td>
</tr>
<tr>
<td>Renal tumours</td>
<td>Dr Sandeep Agarwala</td>
<td>All India Institute of Medical Sciences, New Delhi</td>
<td>sandpag@<a href="mailto:yahoo@hotmail.com">yahoo@hotmail.com</a></td>
</tr>
<tr>
<td>Neuroblastoma and other SNSTumours</td>
<td>Dr Satya Yadav</td>
<td>Medanta — The Medicity Hospital, Gurgaon</td>
<td><a href="mailto:satya_1026@hotmail.com">satya_1026@hotmail.com</a></td>
</tr>
<tr>
<td>Liver tumours</td>
<td>Dr Priyakumari T</td>
<td>Regional Cancer Centre, Trivandrum</td>
<td><a href="mailto:drpriyarcc@gmail.com">drpriyarcc@gmail.com</a></td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>Dr Ashwin Mallapatna</td>
<td>NarayanaNethralaya, Bangalore</td>
<td><a href="mailto:ashwimc@gmail.com">ashwimc@gmail.com</a></td>
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<tr>
<td>Soft tissue sarcoma</td>
<td>Dr Siddharth Laskar</td>
<td>Tata Memorial Hospital, Mumbai</td>
<td><a href="mailto:lasikars2000@yahoo.com">lasikars2000@yahoo.com</a></td>
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<td>Ewing sarcoma and PNET</td>
<td>Dr Bivas Biswas</td>
<td>Dr. BRA Institute Rotary Cancer</td>
<td><a href="mailto:bivasbiswas@gmail.com">bivasbiswas@gmail.com</a></td>
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<tr>
<td>Osteosarcoma</td>
<td>Dr Tushar Vora</td>
<td>Tata Memorial Hospital, Mumbai</td>
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<tr>
<td>Germ cell tumours</td>
<td>Dr Venkat Radhakrishnan</td>
<td>Cancer Institute, Chennai</td>
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<td>Histiocytosis</td>
<td>Dr Gaurav Narula</td>
<td>Tata Memorial Hospital, Mumbai</td>
<td><a href="mailto:drgauravnarula@gmail.com">drgauravnarula@gmail.com</a></td>
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<tr>
<td>Epithelial &amp; rare tumours</td>
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<td>Tata Memorial Hospital, Mumbai</td>
<td><a href="mailto:maya.prasad@gmail.com">maya.prasad@gmail.com</a></td>
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<td>Hematopoietic stem cell transplantation</td>
<td>Dr Sunil Bhat</td>
<td>Mazumdar Shaw Cancer Center, Narayana Health City, Bangalore</td>
<td><a href="mailto:sunilbhat_9@hotmail.com">sunilbhat_9@hotmail.com</a></td>
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<tr>
<td>Supportive care</td>
<td>Dr Brijesh Arora</td>
<td>Tata Memorial Hospital, Mumbai</td>
<td><a href="mailto:brijesh.arora@gmail.com">brijesh.arora@gmail.com</a></td>
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<tr>
<td>Access to care</td>
<td>Ms Shalini Jatia</td>
<td>Tata Memorial Hospital, Mumbai</td>
<td><a href="mailto:shalinijatia@hotmail.com">shalinijatia@hotmail.com</a></td>
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<tr>
<td>Epidemiology</td>
<td>Dr Ramandeep Arora</td>
<td>Max Super Speciality Hospital, New Delhi</td>
<td><a href="mailto:childhoodcancer@gmail.com">childhoodcancer@gmail.com</a></td>
</tr>
<tr>
<td>Late effects</td>
<td>Dr Gauri Kapoor</td>
<td>Rajiv Gandhi Cancer Institute and Research Center, Delhi</td>
<td><a href="mailto:kapor.gauri@gmail.com">kapor.gauri@gmail.com</a></td>
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</table>

PNET — primitive neuroectodermal tumour, SNS — sympathetic nervous system.
this workforce effectively and efficiently is key in addressing this. Perhaps, the greatest challenge to transforming the landscape of pediatric oncology research in India lies in overcoming inertia to collaborate, transforming long-held views of skepticism and generating self-belief. Providing leadership, being inclusive, and developing regular channels of communication, can achieve this. Successful development and execution of the first few InPOG clinical trials would go a long way in bringing about this change.

It is important to emphasize that InPOG is not and does not intend to be a funding body. It is expected that the individual chief investigators will be responsible for obtaining the necessary funding for their respective studies. InPOG merely serves to bring the researchers together and conduct research in an organized and disciplined manner, and assist in developing multi-centric contribution.

4. The way ahead

These are but the first steps of an exciting collaborative journey ahead. The early signs look promising with great interest among the pediatric oncology community, the allied specialists as well as other stakeholders like the parent support groups. In the short term, the InPOG executive aims to facilitate the optimum functioning of each disease subcommittee, secure support and funding for a common clinical trial management system which could be used by any InPOG study, and develop a manuscript monitoring committee. Funding sources being explored include the government, philanthropic organisations as well as the pharmaceutical industry. A dedicated section on the PHO IAP webpage (www.phoindia.org) is also being planned. Ultimately the success of this endeavor would be measured by the progress it makes in improving the outcomes of children with cancer in India.

Conflict of interest statement

The authors declare that they have no conflict of interest.

Table 2

Current portfolio of InPOG studies.

<table>
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<th>InPOG number</th>
<th>Study title</th>
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<td>Ongoing InPOG studies</td>
<td>A collaborative study for newly diagnosed childhood Hodgkin’s lymphoma patients in India</td>
<td>Jagdish Chandra</td>
<td>Recruitment Commenced – Aug 2015 Centres recruiting – 18 Patients recruited – 61 (target 350) Expected duration of recruitment – 3 years</td>
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<tr>
<td>InPOG-ALL-15-01</td>
<td>An Indian Childhood Collaborative Leukemia Group multicentre national standardization study for newly diagnosed acute lymphoblastic leukemia</td>
<td>Vaskar Saha</td>
<td>Recruitment Commenced – Feb 2016 Centres recruiting – 7 Patients recruited – 0 (target 2240) Expected duration of recruitment – 4 years</td>
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<td>InPOG studies in development with provisional registration</td>
<td>A Prospective Open-labeled Randomized Control Trial of Proactive Enteral Nutrition Versus Standard of Care in Children with Cancer and High Nutritional Risk</td>
<td>Brijesh Arora</td>
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<td>InPOG-LE-15-01 (P)</td>
<td>The Indian Childhood Cancer Survivorship Study (C2S study): After treatment completion registry of childhood cancers – Phase 1</td>
<td>Rachna Seth</td>
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<td>InPOG-ACC-15-01 (P)</td>
<td>Multi-site Prospective Study to Determine Household Out-of-Pocket Expenditure Incurred by Families of Children Newly Diagnosed with Cancer in India (HOPE Study).</td>
<td>Ramandeep Singh Arora</td>
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<td>InPOG NHL-15-01 (P)</td>
<td>A Retrospective Multicentric Study of Contemporary Epidemiology &amp; Outcome of Childhood B-NHL in India</td>
<td>Anita Trehan</td>
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