Background Paper

On the Merger of the Pediatric Cancer Clinical Trials Cooperative Groups

A Personal Perspective
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Introduction

This background paper has been prepared at the request of Sharyl Nass, PhD, IOM Study Director for the Committee on Cancer Clinical Trials and the Cooperative Groups. In order to provide the committee some perspective on issues relating to improved efficiencies which might result from reorganizing the group program, it was deemed worthwhile for the committee to review the experience with the consolidation and merger of the four pediatric cancer cooperative groups into one. As there is nothing published about why and how we accomplished the merger nor has there ever been a formal evaluation of the results achieved, this background paper of necessity offers my personal perspectives as past Chair (1992-2001) of the Pediatric Oncology Group (POG) and one of the principals deeply involved in the process. The opinions expressed are thus mine, and I take responsibility for the points of view expressed and for any errors of omission.

Historical Background of the Pediatric Cancer Groups

The first and longest established pediatric cancer clinical trials group was the Children’s Cancer Group (CCG), one of the original groups formed in the 1950’s, previously known as CCGA or Group A, to distinguish it from Group B, the forerunner of CALGB. The Southwest Cancer Chemotherapy Study Group, the forerunner of SWOG, was originally organized as a pediatric oncology group in 1956 and only later expanded to include evaluation of adult malignancies. In 1979/80, the pediatric division of SWOG elected to separate and seek independent status, and thus POG was formed. POG was promptly joined by all but one of the former members of the pediatric division of CALGB. Some large pediatric cancer centers previously not active in cooperative group activities also joined POG, including St. Jude Children’s Research Hospital, Stanford, the Dana Farber and a number of Canadian institutions and groups in Switzerland, the Netherlands and Australia. POG flourished and grew to virtually equal size as CCG in terms of institutional members and patient accruals. Both POG and CCG were multidisciplinary, multi-disease groups. There were meantime two single-disease pediatric cancer cooperative groups, the National Wilms’ Tumor Study Group (NWTSG) and the Intergroup Rhabdomyosarcoma Study Group (IRSG) whose members actually were comprised of the investigators and member institutions of both POG and CCG. NWTSG and IRSG each maintained separate group statistical centers, had their own Chairs, and underwent separate peer review. By the late 90’s, the four pediatric groups had a long history and tradition of both friendly competition and close collaboration.

Reasons for the Merger/Why we did it

I still have a fairly vivid recollection of the meeting we had in July, 1998, at O’Hare Airport where we got the idea. The leadership of all four of the pediatric groups, including the Chairs, vice-Chairs, Statisticians, and Group Administrators, were gathered to work on how we could improve the efficiencies of the intergroup process. We decided the best way was simply to eliminate the intergroup mechanism entirely and just merge
and work together. I seem to recollect that I was the first to voice the idea and others quickly agreed. We reached a verbal agreement to merge in about twenty minutes. There was no external pressure. I think it’s fair to say that we surprised NCI and all of our members with the news of our decision.

Besides long-standing frustration with the cumbersome intergroup process, there were actually a number of reasons for our decision:

1) **Strength in numbers.**
Because of significant success in treating all forms of childhood cancers, survival rates had successively improved such that larger and larger numbers of patients were needed to enroll on randomized clinical trials in order to achieve reasonable study objectives of demonstrating significant improvements in overall results within a reasonable time frame. The days of single institution randomized trials, like those conducted at St. Jude’s in the 60’s and 70’s, had long past. Given the relative rarity of pediatric cancers in general, and the increasing sophistication of stratification of trials into smaller and smaller risk-adapted subgroups, it became obvious and necessary to increase collaboration in order to accrue sufficient patients. POG and CCG were already working together in many areas, doing intergroup trials in Wilms’ tumor, rhabdomyosarcoma, medulloblastoma, Ewing’s tumor, osteosarcoma, hepatoblastoma, and germ cell tumors, and we were beginning to consider intergroup studies for infant leukemia and neuroblastoma. It was clear we needed almost every institution and child with cancer in North America to mount practically any randomized study. So we figured we might as well just merge to gain the strength in needed numbers of cases. By merging, we also had the added advantage of providing seamless geographic coverage of North America, enabling us to tackle epidemiologic studies not possible as separate entities, like a national children’s cancer registry. We also figured that we gained and grew stronger in investigator talent and resources, by, in effect, creating a monopoly.

2) **Informatics**
At the time, NCI was requiring all of the cancer cooperative groups to make extensive changes to their informatics infrastructure, to adopt common toxicity codes and data dictionaries, streamline and harmonize data reporting, and migrate from paper to electronic forms. This work was both onerous and expensive, and we reasoned we should work together to accomplish all the upgrades to our informatics systems. Balkanizing our efforts in informatics and data management seemed stupid.

3) **More Efficient Relations with Industry**
Just like the adult groups, the pediatric groups relied on the pharmaceutical industry to get promising new agents for testing. This process of working with industry was inherently challenging because the pharmaceutical industry had so little interest in developing and licensing drugs for childhood cancers because of the small market. Some of us also suspected industry of playing one group against another to try to lowball contract terms for support of clinical trials. So we reasoned that by providing a single
source, single point of service, and the promise of increased accruals and more rapid completion of Phase I-II trials, we would be much more effective in our relations with industry.

4) Better relations with parents, the public, and advocacy groups

By working together, we were certain that we could articulate a stronger case for pediatric cancer clinical trials. Our experience had been that parents and the public were confused about POG and CCG and why there were two groups and what were the differences. At a local level for individual patients and families, this often created confusion in obtaining second opinions. Simply going across a city like Chicago could result in two entirely different recommendations for treatment of acute leukemia, for example. Committed individuals and foundations desirous of supporting research to cure children’s cancer were also confused about where to direct their gifts to have the greatest impact. Support was splintered. Consolidating our efforts solved these problems.

The Transition Period/ How we did it/Challenges encountered

Making the decision to merge the pediatric groups was the easy part. The really hard part came with actually accomplishing the merger. This took us three years and proved to be very challenging indeed. Perhaps the biggest challenges were in developing trust and merging our very different group cultures. Other major challenges we encountered were the following:

1) Keeping the groups going while we merged

We couldn’t exactly call a “time-out”. Together we had four groups to run, large staffs to manage in multiple group operations headquarters and statistical offices, grants and financial management obligations, studies to analyze and publish, audits that had to continue, meetings to plan, scores of protocols in development and an even greater number open and active or in follow up, and literally thousands of patients enrolled on study. On top of all these usual and customary tasks of cooperative groups, we had to add all the extra work of the merger, which involved development of a memorandum of understanding, creation of an interim governing council, creation of a new constitution, transitional committees for every disease and discipline, a new membership committee to review the performance and qualifications of every institutional member, new rosters, greatly increased communications, and many additional interim meetings. And we had to do all this work without extra staff. NCI did, however, provide some additional funding to cover some of the additional travel costs associated with interim meetings. But no extra staff were hired, and we had to face the daily challenge of trying to retain our valued staff who were worried that their jobs would be eliminated by the merger. And their worries were real. I eventually had to wind down and close the entire POG operations office in Chicago, while staggering the layoffs to keep the essential work going until the new group was functional.
2) Establishment of an interim executive committee, ‘aka’ the Transition Team

Clearly we needed a mechanism to reach decisions for the new group (which we actually called TNG for a while, for The New Group, until we could come up with a name for it). So our first task was to create a Transition Team. In order to provide for fair and equal representation and to ensure stakeholder buy-in, this committee included the group chairs, vice chairs/executive officers, administrators, and group statisticians for each of the four groups, and the heads of the discipline committees of surgery, pathology, radiation therapy, nursing, and the CRAs for both POG and CCG. The Chairmanship of this committee was rotated between the group chairs. The meetings were often intense, so we had another committee, i.e. the “transition monitoring committee”, whose members sat in on our team meetings as observers and whose job it was to provide two-way communications for us with the membership-at large. The Transition Team governed TNG until a new Group Chair and Executive committee were seated in the spring of 2001. The transition in group governance followed a democratic process involving first drafting and ratifying a new constitution (no small task, completed by December 1999), voting on a Nominating Committee by members of the Voting Body, comprised of all the PIs of the member institutions (February 2000), screening and preparation of a slate of candidates for Group Chair (May-Sept 200), presentation of Chair candidate platforms at the Fall (November 2000) group meeting, followed by balloting by all the members.

3) Dealing with the merger of the groups’ statistics and data management operations

A major task we faced was reaching some consensus regarding group data management and statistics. Maintaining the integrity of the legacy data from the four groups was of major importance. Someone had to be in charge. To help us with reaching this decision, we sought external guidance and convened an ad hoc site visit team, composed of experts outside of the pediatric groups and chaired by Steve George, Group statistician for CALGB, to visit the statistical offices in Gainesville (POG), Arcadia (CCG), and Omaha (IRSG). (I seem to recall that NWTSG had no interest in taking over the responsibility for the statistics and data management operations of TNG.) Steve’s task was to provide the Transition Team with an assessment of the strengths and weaknesses of the offices and make a recommendation. This report occurred at an interim meeting in Montreal which was a difficult one. The Transition Team voted (narrowly) in keeping with the site visit assessment that the POG office was the choice, but the Group Statistician selected to lead TNG was Jim Anderson, the incumbent statistician for the IRSG. What we wound up with was a distributed network of statistical offices and staff. In the process we lost cohesion and some valuable people. And many legacy studies have never seen the light of day.

4) Merging the science of the group
This required merging of disease committees which historically had been competitive, often based on competing scientific strategies developed over the course of serial studies. For example, POG had consistently pursued a more biologically-based, lineage-specific strategy in ALL with reliance on anti-metabolite based treatment backbones. In contrast, CCG had different risk-definitions, lumping both B-precursor and T-Cell ALL together, with treatment strategies based on a BFM-type backbone. Getting the groups to come together and agree on a disease-specific strategies going forward sometime seemed as daunting as reaching an agreement on Middle East peace. Adding to the tension, the need to agree on scientific strategies and define the investigator leadership for disease and study committees was a non-trivial exercise which was occurring on a timeline created by the pressure of knowing we had to prepare the U10 progress reports and a new unified grant application for future funding. Of necessity, compromises were reached which did not leave everyone happy.

5) Merging the money

There was a lot of work involved with revised budgeting for the group U10 grants during the transition, but the real problems (at least for some of us involved) were in dealing with the separate foundations which CCG and POG had established for private money. POG and CCG had established very different structures for their 501© 3 corporations. POG’s was very simple, with no additional paid staff. As Group Chair, I was the Foundation president, and the Executive Committee was the Board of Directors. The POG group grants and contracts were run through Northwestern and the University of Florida. In contrast, Denman Hammond, the past Chair of CCG, had established a corporation, the National Children’s Cancer Foundation (NCCF) to act as the grantee organization for CCG to capture all the indirects. Dennie was the President of NCCF and there existed a lay Board of Directors. NCCF offices were co-located with the CCG Group Operations and Data Management Center in Arcadia. NCCF had a fairly large staff, some with six-figure salaries, and engaged in active fund-raising from the public. In essence, POG had to merge with both NCCF and CCG, and the due-diligence required to try to unravel the finances proved very trying. I well recollect closing out our POG foundation in Illinois and writing a check to NCCF for the balance of our funds (roughly a quarter of a million dollars).

What has been the outcome?

The main outcome of the merger of the pediatric groups is that we actually did it. It is hard to overstate the vision, dedication and spirit of collaboration required to pull this off. Once embarked on the pathway of consolidation, there was no thought of reversing our path. We overcame all of the obstacles and created the Children’s Oncology Group (COG), which is now the world’s largest childhood cancer research organization, united with NCCF under the umbrella 501©3 to form CureSearch, with offices in Arcadia, Gainesville, Omaha, and Bethesda and 235 member institutions all over the US and Canada plus five other countries. There are more than 5000 individual members.
Are there any lessons to be learned from the merger of the pediatric groups which might apply to the current cooperative group program?

The committee may wish to consider the following sorts of questions in their deliberations regarding changes in the structure of the current cooperative group program:

What is the right group size? Is COG too big? I don’t think so. The increasing need to have greater sophistication in trial designs stratified by biomarkers and risk for relapse, for instance, is making it increasingly difficult for individual adult groups to mount definitive studies of treatment and prevention, even for fairly common adult malignancies. Collaboration becomes essential for less common tumors and for smaller stratified patient sub-populations.

What’s the best model for the sponsor/grantee relationship? Universities are not necessarily the best grantee organizations for a cooperative group. Should the public-private partnership model used by COG of a private grantee corporation be encouraged? NSABP already runs its grants through its foundation. Could the Coalition of National Cancer Cooperative Groups play a larger role as an umbrella corporation for the groups? The Coalition already holds the contract for the CTSU.

How many groups are needed to do trials quickly and efficiently? If there are to be fewer trials, as some have recommended, should there not be fewer groups? Now that sites can enroll through the CTSU on any open trial, and trials are prioritized by steering committees, does it make sense for there to be four adult multi-disciplinary, multi-disease groups (CALGB, ECOG, SWOG, and NCCTG), each with its own headquarters and statistical centers, undergoing separate peer review? Does it make sense for there to be two surgical groups, for both ACoSOG and NSABP to co-exist? Should peer-review be the mechanism to reduce the number of groups? Or should some preemptive actions be considered? We came to the conclusion that, in some respects, POG and CCG were redundant. And we also thought it likely that NWTSG and IRSG were going to experience problems in the next round of peer review if they went it alone. Judging by our experience, though, I think we never would have succeeded with our consolidation if the decision to do so had been presented to us as an ultimatum from NCI. We succeeded because it was our idea, not theirs. If there can be some way to make the prospects for consolidation advantageous to the groups, i.e. a carrot versus a stick, perhaps the likelihood of reduction in the number of groups would increase.