Multicentre Research in Pediatric Palliative Care: A Comparison of Processes across Multiple Research Ethics Boards*

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ABSTRACT

Methodological and clinical challenges justify the need for multicentre studies in order to undertake research in pediatric palliative care. However, multicentre studies require obtaining approval from numerous Institutional Review and Research Ethics Boards (REB). This report documents a research team's experience when applying for ethical approval for a multicentre study in pediatric palliative care. Based on quantitative and qualitative data, results of this retrospective analysis revealed a variable and overall lengthy review process. Large between-site variations in the length of time from application submission to approval were evident, with a tendency for clinical sites to take longer to grant approval. Institution-specific requests, clarifications on procedures to protect participants, and grammatical changes constituted the requests for changes from REBs. A lengthy ethics review process could result in increased budget costs, study delay, and the inability to demonstrate progress to an external funding agency. Recommendations include coordination of REBs' reviews when evaluating one protocol used in multiple sites. Pediatric palliative care researchers also need to factor in the additional time and cost associated with seeking ethics approval from multiple REBs, and to take an active role in educating REBs on the special elements of palliative care research.

A INTRODUCTION

Pediatric palliative care aims to improve the quality of life of children living with a life-limiting illness by addressing the child and family's physical, psychosocial, and spiritual needs. It is vital that an evidence base be established to guide the practice of pediatric palliative care (1-3). However, research in the field has been fraught with challenges such as the patients' unpredictable illness trajectories (4) and complex debilitating symptoms (5) that make research difficult to undertake and cause attrition in research populations. In addition, the small number of patients available and gate-keeping from professionals (3) make research in this area additionally daunting. These factors combine to indicate the need for multicentre studies (6) which implies the necessity to seek research ethics approval from multiple Institutional Review and Research Ethics Boards (REBs). This manuscript reviews the experiences of one research team in applying for ethics approval for a pediatric palliative care multicentre study with the aim of making recommendations to streamline the process.

The difficulties associated with navigating through multiple REBs when conducting multicentre research have been well-recognized (7). It is extremely time-consuming to obtain REB approval for multicentre studies (8-9). The responses from committees also vary – not all will grant approvals right away, and the changes to the protocol requested by different committees may be conflicting (10-12). REBs often prefer contacting the local principal investigator (PI) regarding their concerns instead of directly communicating with the central coordinating site of the multicentre study, even though staff and the study's PI at the central site are often responsible for completing the forms and responding to all REB concerns (8). The high cost associated with

multiple REB applications is often not anticipated, creating the need to seek extra funding to cover costs such as photocopying, postage, and research assistants' wages. Vick et al. (13), for example, noted that more than US$53,000 was spent on staff salary during the ethics process alone in their 14-site study, accounting for 13% of the entire 2.5-year study budget and 24% of the first year's budget.

The paucity of research in the palliative care field implies that REBs may have less experience with research protocols on palliative care compared to those from other clinical areas (14). The nature of pediatric palliative care research which compounds two vulnerable populations, children and the terminally ill, may create further concerns for REBs, translating into an even lengthier review period or a higher likelihood of rejection (15). While there have been articles documenting the challenges of conducting multicentre research (8), none have focused on research in pediatric palliative care. The purpose of the current manuscript is to document one research team's experience when applying for ethics approval for a multicentre study in pediatric palliative care and to propose strategies for streamlining the process of obtaining ethical approval.

A DESCRIPTION OF THE MULTICENTRE STUDY

The multicentre study funded by the Canadian Institutes of Health Research is entitled "Caregiving Parents of Children With Life-Limiting Illnesses: Beyond Stress and Coping to Growth". The primary aim of this research addresses the question "What are the factors that allow parent caregivers to survive and even grow in the face of the stressful circumstances of

caring for a child with a life-limiting illness?" The research team includes seven co-investigators at six different institutions, as well as identified collaborators at remaining data collection sites where no co-investigator was located. Parent caregivers recruited from the six participating children's hospitals or hospices first completed mail-in questionnaires which studied factors related to personal growth during the stressful circumstances of caring for their children. A subset of the participants from the first phase further completed the second phase, in which in-person interviews were conducted to document personal growth experiences of the parent caregivers. To obtain the minimum target of 200 participants, each site was asked to post recruitment posters and to send an information letter to families on their program; some programs opted for one approach only. Recruitment posters were circulated to various associations affiliated with life-limiting illnesses in children and advertisements were placed in some relevant online magazines. Parents who were interested in participating, regardless of the manner in which they heard of the study, were asked to phone a toll-free telephone number and leave a message to which the central study coordinator would respond. This manner of recruitment was designed to avoid any possible perceived coercion from health care practitioners as none would have knowledge of the identity of participants. In addition, the toll-free number meant that potential participants volunteered at no cost to themselves and they could glean additional information from the voice mail recording as well as call any number of times.

B *Procedures for Obtaining REB Approval*

A study protocol was developed and used by the central coordinating site as the basis for completing the ethics approval applications. The research staff at the central coordinating site

identified and contacted the relevant REBs to obtain the application and institutional requirements. All the applications and supporting documents were completed by the central site to the specification of each REB. Local PIs were asked to review the completed application and supporting documents pertaining to their sites. Upon the satisfaction of the local PIs, the applications and supporting documents, tailored to the requirements of each REB, were submitted to the REB by the local PIs. The research staff maintained regular communication with the local PIs with regard to the progress of the applications and responses from the REBs. If revisions or clarifications were requested from the REBs, staff at the central site completed and forwarded the answers to the local PIs who then relayed the requested information to the REBs. During the REB process, the central site research staff kept field notes to track elapsed times in the application process, REB requirements for the applications, and results of the REB review, as well as correspondence with the local PIs and the REBs.

A total of 11 REB applications were prepared for the study: four for academic settings and seven for clinical settings. In an attempt to minimize the number of revisions required for all ethics applications, two academic REB applications were submitted first with two clinical REBs following closely. The first academic submission was for the institution of the project PI; the second was for the academic institution of the research office where the staff was located. The clinical REB applications were submitted to two sites located in close proximity to the research office; both were conditional upon the local academic institution’s approval. By first obtaining approval from two academic institutions, it was hoped that clinical institutions would be amenable to expedited processes.

A RETROSPECTIVE ANALYSIS OF REB APPROVAL PROCESS

Similar to Green et al. (8), this paper constitutes a descriptive review of the process of obtaining ethical approval for a multicentre study pertaining to parental caregiving of a child with a life-limiting illness.

The retrospective analysis of the process utilized both quantitative and qualitative sources of data. Quantitative data were gathered through recording the number of copies requested by each site, the amount of time between submission of the application and receipt of a response from each REB, and the number of revisions requested by each REB; these findings are presented as descriptive statistics. This analysis was done retrospectively as it was not anticipated that the REB approval process would be so time intensive. Hours spent by staff were not tracked from the beginning and proved impossible to track retrospectively. Consequently descriptive statistics on the time for each critical step in the REB process are counted by number of days elapsed rather than staff hours dedicated to the process.

Texts of requests for changes from the various REBs were pooled to ensure that no one institution was identified and these data formed the qualitative component. Qualitative analysis concentrated on the comments made and changes requested by the six REBs that did not give approval in the first instance The text data were analyzed by three co-authors (LJ, KW and SC) using thematic analysis (16) to establish central themes which were then used to enrich the statistical analysis. Illustrative examples will be provided for each theme; quotes will not be used in the reporting of these qualitative results as they would identify the REB making the request.

A RESULTS OF THE RETROSPECTIVE ANALYSIS

The 11 applications were tracked through the preparation and approval process. All applications were eventually approved by the REBs, but the process of obtaining approval varied widely. The number of copies of the application requested by each of the 11 REBs ranged from 1 to 21 (M = 9.91, SD = 8.24). Although the protocol was identical for all sites, five sites processed the application through expedited review based on prior approval (based on a non-expedited process) from the PI's primary academic institution and/or because the study was nationally funded through a process which included scientific review. Of these five sites, two were clinical and three were academic.

The six remaining REBs took longer because each required a full review of the study protocol. Of these six REBs, one was academic and the other five were clinical sites or had joint clinical and academic review boards. Among the sites that underwent a full review, one REB initially allowed for expedited review but subsequently requested a full review due to concerns with the sensitive nature of the study and the recruitment procedures. A secondary internal review was also required for four of the sites.

B *First Submission to Response*

The amount of time lapsed for each critical step in the REB process was counted in number of days lapsed. The first clinical site was omitted from the calculations as its procedure was expedited; it also varied from the other sites in that it mostly concerned hours spent by on- site

staff for recruitment. For the remaining 10 sites, an average of 33 days (*M* = 33.5, *SD* = 22.93, Range = 6-68) elapsed between the time of submission and the first response from the REB. Figure 1 presents the timeline from submission of the application to approval for each of the 10 REBs.

<INSERT FIGURE 1 HERE>

B *Time to Approval*

The average length of time for REBs to grant ethics approval for the study was over 80 days (*M* = 81.9, *SD* = 70.44). The amount of response time from submission to approval for each REB varied widely: from 14 days to more than 200 days, despite applications being based on the same study protocol. Because local PIs were required to submit the applications and revisions at their respective sites, it took time for them to communicate with either the central coordinating site or with their REB. An average of 38.86 days (*n* = 7, *M* = 38.86, *SD* = 32.96, Range = 2-89) elapsed during these communications.

B *Numbers of Queries*

Of the six REBs that requested additional revisions or clarifications of the application, three requested revisions once, two requested revisions twice, and one requested changes to the protocol three times before granting final approval for the study. Within each request for revision

from the six REBs, the number of queries for revision or clarification ranged from 11 to 39, with a mean of 20.16 and a standard deviation of 10.43.

Thematic analysis of the requested clarifications from the six REBs that did not immediately grant approval fell into three categories. These were, ranging from the most to least frequent: institution-specific requests, protection of participants clarifications, and grammatical changes.

B *Institution-Specific Requests*

All REBs made requests specific to their institution. This category of requests occurred most frequently (N = 26) and included administrative details and affiliation requirements, as well as one significant protocol change. Administrative details included requests for the use of institutional letterhead and specific formats for version numbers and dates on all forms. These details had to be tailored for each application. Some REBs inquired if money was being transferred to the institution and they asked for further details; one institution requested an itemized budget even though no money was being transferred to the site.

Many institutional requests concerned researchers' affiliations. Because the study was recruiting through institutions in two countries, several clarifications involved identification of researchers' country of origin. One REB requested that names of all non-local investigators be removed from study materials; this request resulted in the removal of the PI's name from all study documents for that site.

Only one site requested a change to the study protocol itself. This particular board requested that the 1-800 number not be used for their site and that it be replaced by a local number. This change would require the hiring of an additional research assistant to return phone calls for one site and was fraught with many logistical and confidentiality concerns. The REB eventually granted approval based on the original protocol and no changes were made.

B *Protection of Participants Clarifications*

In 13 requests from six REBs, requests pertained to a theme of participant protection. These requests fell into the categories of privacy and confidentiality, staff training, participant distress, and consent. Requests concerning privacy included clarifications or changes in how personal information would be kept confidential and requests about data storage. Concerns were also raised about the research team having access to families on an active palliative care list because of a concern that families might feel coerced if informed of the study by their health care practitioner(s). This concern was raised despite the recruitment protocol being specifically developed to avoid such a situation. Other requests included changes to the information letter explaining the confidentiality process and identification of who would have access to the data or identifying information.

In addition, a number of changes or clarifications pertained to research assistants and staff training. Background information on the research staff was requested, as well as specific information on who would provide the training to research assistants and in what manner training would be offered. Further information about how the staff would handle distressed participants

was sought by two REBs, and one requested that changes be made to the consent form to include such details.

Consent issues were raised by three of the six REBs. These concerns mostly were due to recruitment of families on active palliative care lists and whether their prior consent would be obtained or needed. Concerns regarding consent also included requests for changes to the consent form to highlight the option to skip questions and to allow participants to indicate their preference about being audio-taped during their interview. In addition, clarification was sought with regard to consent for the second phase to ensure that the lack of return of the surveys from phase one would constitute refusal to be contacted for the follow-up interview.

B *Grammatical Changes*

Grammatical changes were requested by four of the six REBs. For the most part, these changes were related to word choice and the deletion of sentences or paragraphs. The most common request was to change the original recruitment poster wording of “we require” to “we are seeking”. One institution had 11 grammatical requests that ranged from changing words to deleting entire paragraphs from the information letter.

A DISCUSSION

The purpose of the current descriptive report was to document the ethics approval process for a multicentre study in pediatric palliative care in order to make recommendations to streamline the

process for other researchers. The results indicate that considerable time and effort was devoted to obtaining approval from these various Institutional Review and Research Ethics Boards.

Originally, the team anticipated that ethics approval for this study would take six months and that recruitment would begin in the latter half of the first year. However, because recruitment could not begin until ethical approval had been granted at every institution, the study did not begin accrual until well into the second year of its three year funding. Not only did this lengthy process have budget implications, but it also limited the research team's ability to demonstrate progress because the entire timeline of the project was delayed by a year.

Despite the protocol being approved at the two main academic institutions, expedited review was not allowed in most cases. Of particular note, the sites that required the most time and the most iterations of applications were clinical or combined clinical/academic REBs. However, two of the most quickly approved sites were also clinical, both based on the prior approval from an affiliated academic institution and/or the fact that the funding had been obtained via a national peer review process.

Each time a REB requested clarification on the application, time was spent preparing the changes and communicating with the local PI in order to apprise them of the revisions. Green et al. (8) note concerns about the requirement of ethics review boards to have local PIs as a contact person as it increases the time and cost of the ethics application process. Our research team had less difficulty in identifying the local PIs than Green et al. (8) but the necessity of communicating with the local PI instead of directly with each REB did increase the time for each application.

The qualitative data addresses the content of the requests and clarifications sought by the REBs that took the most time for granting approval. Of note, the changes sought were mostly institution-specific, focused more on the research procedures in each institution than on the ethical treatment of participants. While the grammatical changes seem trivial and represent the smallest number of requests, these were nonetheless very difficult to anticipate and were time consuming to rectify because every site required new versions of documents to have updated version numbers and dates on the forms. Although there was one REB that requested a significant change to protocol, none of the changes in either phase of the study actually resulted in procedural changes such as those that Green et al. (8) experienced: modifications of the recruitment or research methods.

While there have been concerns about the role of REBs as gate-keepers (17), especially in pediatric palliative care (18), the experience of this research team demonstrated that requests for changes in the ethics applications may have more to do with the institution's role in the research than about protection of the research participants. The site that required its local contact be solely identified is an example of concentration on institutional matters, potentially at an increased risk to participants if they are only provided with partial information. When the local person is identified as the PI, the research is misrepresented– the PI is the person who holds the ultimate responsibility for the conduct of the project and to not identify this person as such is misleading.

A limitation of this paper is that the hours spent by research staff preparing and processing the applications was not tracked because the research team did not anticipate the process would take as long as it did and saw no reason to track this time.

A RECOMMENDATIONS AND CONCLUSION

This paper reported on data collected about the process of gaining ethical approval for a multicentre study in pediatric palliative care. These results are significant as they hold implications for research funding. From this experience, the research team found that when preparing proposals for subsequent multicentre studies it is necessary to factor in the extra time and financial resources needed to seek ethics approval from multiple REBs. It is recommended that other researchers consider this approach when conducting a multicentre study. In addition, it is advisable to track the numbers of hours spent as well as the procedures when undertaking multicentre ethics applications.

The wide variation in the procedures of clinical sites was striking. The process could be facilitated by having REBs coordinate their review in a more streamlined manner when evaluating the same proposal used in a multicentre study. One clinical site in this process serves as an excellent example of a simplified procedure: the one that was omitted from the statistics because of its expedited process. Given the peer review process for national funding and the prior full approval at an academic institution, this clinical site concentrated its review on the related staff hours required for recruitment through their organization. On a wider scale, a national or international process may be needed for REBs to clarify what their role is and to have

consistency in processes. Efforts have been made to implement various types of centralized ethics review systems, either nationally or regionally, in both North America and other countries such as the United Kingdom (19-20). While not without criticism (21-22), a centralized ethics review system specifically devoted to multicentre research may help unify the administrative aspect of ethics application such as the format of the forms or the number of applications to be submitted, so that the REB can re-divert its focus onto examining the possible ethical issues with a study. (18)

In addition, it seems necessary for pediatric palliative care researchers to take an active role in educating REBs on the special elements of palliative care and the issues they face when conducting research, so that REBs can make more informed decisions about the study's scientific merit, as well as its risks and benefits.

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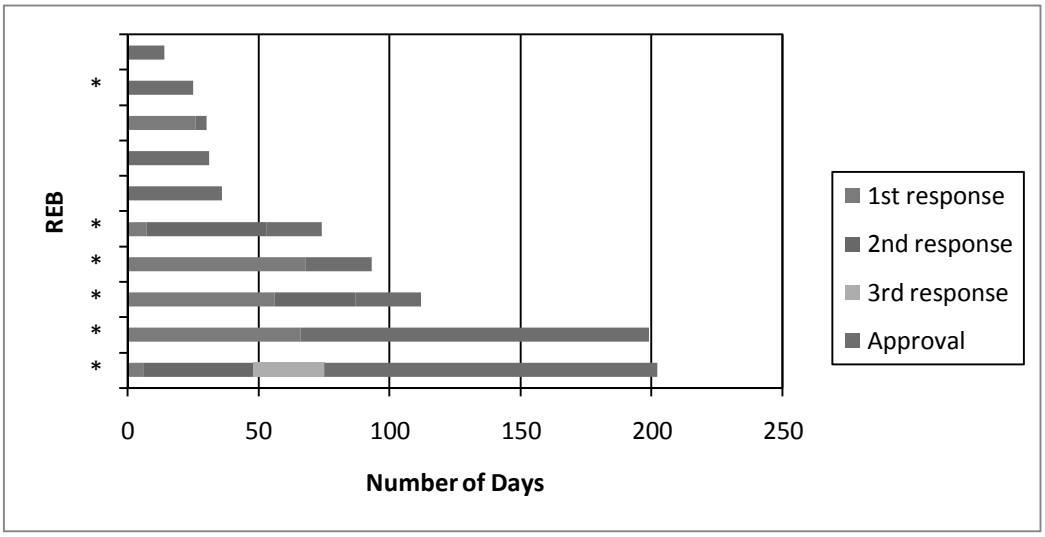
Figure 1

Timeline from Submission of the Application to Approval for REBs



* indicates a clinical or combined clinical/academic REB