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Strategies to Maximize Enrollment in a Prospective Study of Comatose Children in the Pediatric Intensive Care Unit

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Abstract

Objective—To analyze barriers to recruitment encountered during a prospective study in the pediatric intensive care unit and evaluate strategies implemented to improve recruitment.

Design—Prospective observational study of continuous EEG monitoring in comatose children.

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Setting—Pediatric intensive care units at four North American institutions.

Patients—Patients with a Glasgow Coma Score ≥ 8 for at least an hour.

Interventions—Four strategies to increase recruitment were sequentially implemented.

Measurements—Enrollment rates before and after implementation of novel recruitment strategies.

Main Results—The baseline enrollment rate was 2.1 subjects/month, which increased following the single-site introduction of real-time patient screening using an online dashboard (4.5 subjects/month), deferred consenting (5.2 subjects/month), and weekend screening (6.1 subjects/month). However, the subsequent addition of three new study sites was the greatest accelerator of enrollment (21 subjects/month), representing a 10-fold increase from baseline ($P<0.0001$).

Conclusions—Identifying barriers to recruitment and implementing creative strategies to increase recruitment can successfully increase enrollment rates in the challenging ICU environment.

Keywords

clinical trials; enrollment; critical care; child; recruitment; deferred consent

INTRODUCTION

Timely recruitment into prospective studies in the Pediatric Intensive Care Unit (PICU) is challenging. Although historical data can be used to estimate how many patients will be eligible for a study, many unforeseen factors can reduce enrollment such as timely identification of potential research subjects and communication of this to the research team, availability of appropriately trained research team members, challenges in obtaining timely parental consent and a low number of potential subjects at a single institution. Slower than expected enrollment can delay study timelines, increase costs, and threaten successful study completion.[1–4] Recruitment of children poses particular challenges because surrogate consent is required.[5–8]

In the following report, we describe several strategies used to successfully improve recruitment in the Detecting Nonconvulsive Seizures Among Critically Ill Children (DETECT) study.

METHODS

DETECT is a prospective observational cohort study of comatose children in the PICU that employed 48 hours of continuous EEG (cEEG) monitoring on a clinical or research basis to quantify seizures, the majority of which are known to occur without clinical signs.[11] All cEEGs were reviewed intermittently according to institutional clinical guidelines and the results were communicated to the treating physicians who were free to initiate appropriate therapy. The primary inclusion criterion was a Glasgow Coma Score (GCS) ≥ 8 for a minimum of one hour at the time of screening, regardless of coma etiology. Since a patient's level of consciousness could fluctuate, patients were screened for study inclusion multiple

times during their ICU stay. All screening and consenting was performed by research personnel after permission to approach a family was granted by the treating physician. The DETECT study received approval from the research ethics review boards at all participating institutions. Written informed consent was obtained from a legal parent or guardian of all participants.

DETECT enrollment began in January 2010. Over the subsequent 18 months, only 38 subjects had been enrolled (2.1 subjects/month), much less than our anticipated enrollment rate of 10 subjects per month. Improving the enrollment rate was urgently required for successful study completion. This report describes the process used to identify barriers to recruitment and develop strategies to improve the enrollment rate, critically evaluates the success of these strategies and discusses their potential applicability to other prospective studies in the PICU.

IDENTIFYING BARRIERS TO RECRUITMENT

Analysis of the study's interim CONSORT diagram (Fig. 1) revealed several barriers to recruitment. At that time, 240 patients had been screened, 91 of whom were eligible for the study. The most common reasons for not enrolling patients were parent or guardian unavailability (36%), consent refusal (29%), and research staff unavailability (13%). Furthermore, we noted that among the 36 eligible patients already undergoing clinically-ordered cEEG (who could be approached for consent retroactively), 26 (72%) were enrolled, whereas among the remaining 55 eligible patients not already undergoing cEEG (who required informed consent before research cEEG could be initiated), 12 (22%) were enrolled. In this latter group, the GCS often improved prior to consent being obtained, at which point patients were no longer eligible for the study.

Intermittent Screening—Initially, patients were being screened for eligibility twice daily (morning and afternoon). However, we observed that some patients experienced fluctuations in their level of consciousness, such that their GCS declined to 8 only in between scheduled screening times. By analyzing the electronic patient record, we identified the patterns of coma duration for all potentially eligible PICU patients. According to this analysis, 476 patients had actually been eligible for the study, however our twice-daily screening had only identified 240 of these patients (50.4%).

Parent/Caregiver Availability for Consenting—Among patients who were not already undergoing clinical cEEG monitoring, our largest barrier to recruitment was the unavailability of parents or guardians despite multiple meeting attempts. Without their informed consent, we were unable to initiate research cEEG monitoring in a timely fashion. By the time consent could be obtained, some patients' GCS had improved making them no longer eligible for the study, or substantial time had elapsed between coma onset and initiation of cEEG monitoring, potentially biasing our ascertainment of nonconvulsive seizures.

Weekday-Only Screening—Initially, patients were screened on weekdays between 9am – 5pm. Patients who became eligible over the weekend were missed unless they were still

eligible on Monday morning, in which case enrollment was substantially delayed after coma onset.

RESULTS

STRATEGIES TO IMPROVE RECRUITMENT

By employing the following strategies, over the subsequent 2 years, we were able to meet our goal of enrolling 266 subjects across four study sites. Figure 2A illustrates the cumulative and monthly study enrollment and the timing of the various strategies implemented to improve recruitment. The enrollment rate increased from baseline (2.1 subjects/month) following each recruitment strategy implemented at SickKids starting with real-time patient screening (4.5 subjects/month), deferred consenting (5.2 subjects/month) and weekend screening (6.1 subjects/month). However the addition of the three new study sites was the greatest accelerator of enrollment, increasing the rate to 21 subjects/month. Implementation of new recruitment strategies overall was associated with a significant increase in enrollment rate, ($P<0.0001$, Kruksal-Wallis test), but only following the addition of new study sites was there a significant increase in enrollment rate from baseline ($P<0.0001$, Dunn's test).

Real-time Screening Dashboard—To improve upon our intermittent screening practice we created an online real-time screening dashboard at SickKids. (Supplementary Fig 1.) The dashboard was a custom web application that continually pulled GCS data from the electronic patient record and highlighted potentially eligible patients. Using this dashboard, the study coordinator could identify patients as soon as they became eligible, expediting consenting, enrollment and cEEG initiation. Furthermore, the dashboard increased the likelihood that patients who experienced shorter periods of coma would be identified and approached.

Deferred Consenting—Because cEEG is a noninvasive, minimal-risk procedure, we sought and obtained permission from the SickKids Research Ethics Board to use a deferred consenting protocol when parents/guardians of eligible patients were not present in hospital. Deferred consenting permitted initiation of research-based cEEG monitoring when parents or guardians were not present, with consent being obtained as soon as they arrived in hospital (telephone consent was not permitted). Waived consent was not considered because elements of the study required active participation of family members (e.g. baseline and follow-up Vineland questionnaires). Prior to the implementation of deferred consenting, 36% of patients eligible for research cEEG (20/55) were not enrolled because parents or guardians were not present. Deferred consenting resulted in enrollment of 14/15 additional patients eligible for research cEEG. In one instance, parents subsequently declined study participation, the patient was withdrawn from the study and all data was destroyed.

Weekend Screening—Weekend screening was implemented at SickKids to permit eligibility assessment 7 days a week, ensuring a larger and more representative patient sample. Although weekend screening was more burdensome for study coordinators, it

proved to be effective: 13 additional eligible patients were identified, 11 of whom were enrolled at a cost of \$94 per additional subject enrolled.

Study Expansion—The final strategy used to increase the enrollment rate was to invite additional institutions to participate. Although this involved many logistical hurdles including contract negotiations, local IRB approvals, and multiple site visits for training and auditing, this strategy resulted in recruitment of 90 additional subjects over 11 months. Furthermore, including multiple institutions resulted in a more diverse study population, thereby increasing the generalizability of our findings.

DISCUSSION

The four strategies used to successfully increase the enrollment rate in the DETECT study are widely applicable. The real-time screening dashboard strategy could be implemented for any study involving inclusion criteria that are measured continuously and recorded to an electronic medical record. Prior studies have reported increasing enrollment rates by up to 50% by matching the medical record with enrollment criteria, some of which have used fully-automated alerts.[3, 13–16]

Prior studies have reported that between 33% and 84% of eligible children are not enrolled due to family unavailability[2, 5, 6, 9, 10], and roughly 25% of approached surrogate decision makers do not consent due to stress.[2, 5, 6] The deferred consenting strategy addresses this challenge, and could be implemented for any study that involves a time-sensitive intervention that poses minimal risk to subjects. This strategy requires close collaboration with the hospital's Institutional Review Board and appropriate surveillance of adverse events. Only the SickKids research ethics board approved deferred consenting for this study.

The weekend screening strategy could be applied to any study, provided that study personnel are available. However, in our experience weekend screening yielded the smallest increase in recruitment, at a substantial cost of \$94 per additional patient enrolled. Before weekend screening is implemented, careful consideration should be given to whether the anticipated benefits justify the additional cost and burden on study personnel.

Study expansion was our most effective method of accelerating recruitment, and could be applied whenever similar expertise can be mobilized at additional institutions. This strategy brought additional benefits, including engaging co-investigators with additional expertise, distributing the workload among more team members, and increasing the study's generalizability and potential impact.

LIMITATIONS

Despite the favorable risk-benefit ratio of this study, the initial enrollment rate was low, and this was allowed to continue for 18 months before steps were taken to improve recruitment. More timely recognition of this low enrollment rate would have permitted more timely application of the strategies to improve recruitment. Increasing awareness of the study and increasing clinical demand for cEEG monitoring over the 3.5-year study period may have

also contributed to the increased enrollment rate. However, this effect was likely small because the annual number of clinical cEEGs performed actually remained relatively stable over the course of the study.

CONCLUSION

Identification of barriers to recruitment and application of creative, multi-faceted strategies to improve recruitment can be used to successfully increase enrollment rates in the challenging PICU environment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Interim CONSORT diagram used to identify barriers to enrollment between January 2010 and June 2011. Reasons for not enrolling patients are indicated at bottom.

Figure 2.

A) Cumulative and monthly enrollment in the DETECT study, indicating timing of novel recruitment strategies and addition of new centers. B) Monthly enrollment rates following addition of each new recruitment strategy. Only following the addition of new sites was the enrollment rate significantly increased from baseline.