OBSERVATIONAL STUDY

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The Impact of Extended-Hours Patient Recruitment on Critical Care Clinical Trial Enrollment

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IMPORTANCE: Patient recruitment is a critical factor in running successful and timely clinical trials in the critical care field where the timing of presentation of patients is difficult to predict and the study interventions are often time sensitive.

OBJECTIVES: The goal of this study was to analyze the timing of patient enrollments from previous clinical trials to identify patterns and assess the impact of providing extended-hours coverage on patient enrollment.

DESIGN, SETTING, AND PARTICIPANTS: This was a retrospective cohort study at a tertiary academic hospital in the United States between 2016 and 2024 on patients who were enrolled in five recent critical care clinical trials.

MAIN OUTCOMES AND MEASURES: We reviewed the patient enrollment data. We quantified the number of enrollments during business hours (9 AM–5 PM) compared with outside of business hours and analyzed the frequency of enrollment by day of the week and time of day.

RESULTS: There were 352 patients enrolled between 2016 and 2024 across five clinical trials. A total of 242 patients (68.8%) were enrolled outside of business hours. 72.4% of patients were enrolled during weekdays and 27.6% during weekends. The enrollment pattern did not differ significantly across days of the week, ranging from 45 (12.8%) on Friday to 56 (15.9%) on Thursday. Enrollment from 2 PM to 10 PM accounted for more than 50% of the total enrollments. Recruiting only during business hours would have resulted in an additional 15 years to complete one of the trials.

CONCLUSIONS AND RELEVANCE: A review of our five recent critical care trials showed that nearly 70% of enrollment occurred outside of business hours. Limiting recruitment to only business hours would have resulted in a prohibitively longer time to complete the trials. This analysis provides a strong motivation and rationale for extending research staffing coverage beyond business hours.

KEYWORDS: clinical study; clinical trial; personnel staffing and scheduling; research methodology; research subject recruitment

Conducting clinical trials is a challenging endeavor with a complex array of elements that can influence its success. Among these, patient recruitment is a critical factor that has a profound impact on the success as well as the duration of the study (1–6). Patient recruitment is a resource-intensive endeavor requiring substantial allocation of human resources, time, and budget, influencing study design as well as research group organization (1, 7, 8). Adequately addressing these challenges is important as efficient and timely recruitment is essential in maintaining the momentum of the study. One could argue that researchers have an ethical obligation to ensure that clinical trials are performed in a timely manner to prevent delays in getting potential lifesaving therapies to patients.

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KEY POINTS

Question: What is the impact of providing extended-hours coverage for patient recruitment in critical care clinical trials?

Finding: We reviewed the enrollment data from our five recent clinical trials. Nearly 70% of enrollment occurred outside of business hours (9 AM–5 PM Monday through Friday). Enrollment occurred similarly across day of the week. More than 50% of enrollment occurred from 2 PM to 10 PM

Meaning: Limiting patient recruitment to only business hours would have resulted in a prohibitively longer time to complete the trials. This study provides a strong motivation and rationale for extending research staffing coverage beyond business hours.

In critical care research where studies take place in the inpatient setting, patient recruitment is primarily conducted by in-house clinical research staff including research coordinators, research assistants, and research nurses. These individuals are tasked with managing the recruitment process from screening for potential patients and approaching the patient or their legally authorized representative (LAR) to managing and monitoring the study to ensure that the study protocols are followed. Research staff is typically available in person during business hours spanning 8 or 9 hours (e.g., 9 AM to 5 PM or 9 AM to 6 PM) or extended-hours spanning 12 hours (e.g., 7 AM to 7 PM) (1). However, even with these extended hours, a significant portion of the day is missed, which is particularly important in emergency or critical care studies where the timing of presentation of patients is unpredictable. For studies that require study-related tests or interventions that are time-sensitive, the available recruitment time is further reduced. In addition, it can affect the characteristics of the study participants enrolled in the study such as demographics or disease types that can potentially affect the outcome or the impact of the study (9, 10).

Prior studies have identified that adequate staffing to perform recruitment activities was one of the most important enablers to improve recruitment outcomes (2, 8). A study by Peters-Lawrence et al, reviewing a multicenter clinical study on sickle cell patients that terminated early due to low patient enrollment, showed that a significant portion of missed opportunities occurred during off-hours highlighting the importance of extended coverage (3). However, staffing decisions must consider a number of issues including staff availability, the finances of having staff on call during off-hours as well as availability of other resources such as research pharmacy. Prior studies have shown that recruitment outside of business hours is less common even at major academic and research centers due to issues of resources and economics (11). We hypothesize that a substantial portion of potential study participants present outside of business hours (e.g., 9 AM–5 PM) and therefore providing coverage only during business hours results in missing a large number of potential enrollments.

The objective of this study was to analyze the enrollment data from our previous critical care clinical trials to identify patterns and assess the impact of providing extended-hours coverage on patient enrollment.

METHODS

Study Setting

The Center for Resuscitation Science (CRS) is a clinical research center at Beth Israel Deaconess Medical Center (BIDMC) in Boston, MA. BIDMC is a tertiary academic hospital with about 52,000 emergency department (ED) visits and 15,000 admissions annually. Our group has performed and participated in a number of single-center and multi-site clinical studies.

Staffing Strategy

While we have had several variations of staff scheduling approaches, the following describes a primary strategy used in many of our studies. During the weekdays, the research staff scheduling is broken down into three shifts: A, B, and C. The main difference between the shifts is the hours they cover, and there is no significant difference in their responsibilities. The A-shift spans from 8 AM to 4:30 PM and is in-house covering the study pager to screen for potential study participants as well as performing daily tasks such as reviewing charts and documenting data

from enrolled participants and making follow-up calls. At 3 PM, the A-shift signs out to the B-shift whose shift spans from 3 PM to 8 AM the next day. The in-house coverage portion ends at 11 PM and the overnight call is taken at home. The C-shift is in-house from 9 AM to 5 PM providing support for daily tasks. The weekend call is covered by the B-shift from Friday who is responsible for responding to pages and performing manual screening from home until 8 AM on Monday. There are no in-house staff over the weekend. In terms of pay, the B-shift receives slightly higher hourly pay compared with the A and C-shifts. Also, the staff receive additional compensation if they are required to come in during off-hours. However, the research staff take turns covering each shift so that they are evenly distributed. The staffing schedule is depicted in **Figure 1**.

Participant Screening

Participant screening is performed automatically through the electronic medical record (EMR) as well as manually by reviewing patients' charts throughout the day. The automatic screening is performed by building criteria into the EMR to detect relevant events such as abnormal laboratories or ICU admission requests. When these criteria are met, automatic pages are sent out only to the research staff initially who then review the patient's chart and contact the study investigator (principal investigator or co-investigator) if they

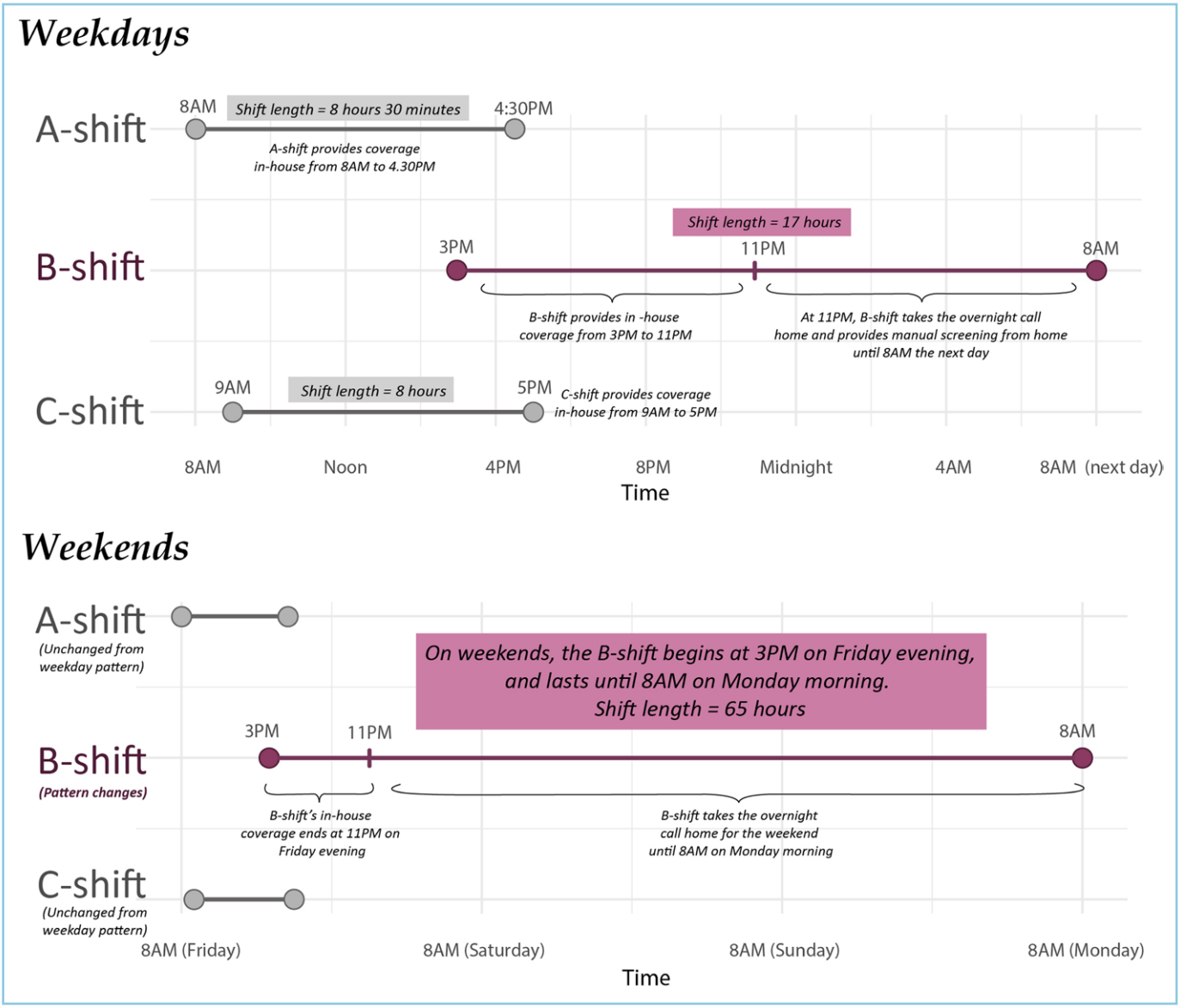

Figure 1. Research staff scheduling used primarily by our group to provide 24/7 coverage.

meet the study criteria. There are cases where automatic screening is not possible such as patients who are already admitted to the hospital or transferred from another hospital. For these cases, the research staff manually screens the ICU and the step-down units for potential participants from 8 AM to 11 PM on weekdays and several times throughout the day during the weekends. Manual screening is not performed overnight.

Review of Patient Recruitment in Recent Clinical Studies

We reviewed patient enrollment data from five critical care clinical trials: Thiamine as a Metabolic Resuscitator after In-Hospital Cardiac Arrest (THICA) (NCT02974257, Institutional Review Board [IRB] Protocol number 2016P000347 approved on 12/28/2016) (12), Ascorbic Acid, Corticosteroids and Thiamine in Sepsis (ACTS) (NCT03389555, IRB Protocol number 2017P000436 approved on 1/3/2018) (13), Thiamine for Renal Protection in Septic Shock (TRPSS) (NCT03550794, IRB Protocol number 2018P000204 approved on 6/12/2018) (14), Thiamine as a Metabolic Resuscitator after Out-of-Hospital Cardiac Arrest (THACA) (NCT03450707, IRB Protocol number 2017P000245 approved on 3/19/2018) (15), and Thiamine as Adjunctive Therapy for Diabetic Ketoacidosis (DKAT) (NCT03717896, IRB Protocol number 2018P000475 approved on 10/23/2018) (16). For all five trials, study protocols were approved by the local IRBs and written informed consent was obtained from all participants. All studies were conducted in accordance with the ethical standards of the local IRBs and complied with the principles outlined in the Declaration of Helsinki (1975). As this current study is a retrospective analysis of previously approved clinical trials, no additional IRB approval was required.

THICA, THACA, and DKAT were single-center studies while ACTS and TRPSS were multicenter studies (14 sites for ACTS and 3 sites for TRPSS). However, only the enrollment data from BIDMC was used for analysis in this work. These studies were selected as they were the most recent critical care trials that used the extended-hours recruitment approach. Therefore, it is important to note that all enrollment data analyzed in this study stemmed from 24/7 coverage. No formal sample size calculation was performed. All patients were enrolled in the ED and the ICU. For THICA, ACTS, TRPSS, and DKAT trials, the enrollment time was defined as the time of signed consent. For THACA trial, the first study drug administration time was used because it was an Exception from Informed Consent (EFIC) study, and some patients received the study drug prior to formal consent. We reviewed the enrollment time of each patient to quantify the number of enrollments during business hours (9 AM to 5 PM on Monday–Friday) vs. off-hours as well as by day of the week and time of day. The overall proportion of enrollments during outside of business hours was computed using a random-effects restricted maximum likelihood (REML) model in Stata 18.5 (StataCorp, College Station, TX) via the "meta" package. The result is presented as a forest plot. Lastly, to demonstrate the impact of the extended-hours recruitment strategy, we compared the actual enrollment progress to what it would have been if business-hours-only strategy was used by removing all enrollments that occurred outside of business hours.

RESULTS

There were 352 patients enrolled (407 consented) between 2016 and 2024 across five clinical trials. The discrepancy between the number of consented and enrolled patients is due to some patients ceasing to meet inclusion criteria and/or meeting exclusion criteria after providing initial consent. A summary of these trials is shown in **Table 1** and the time of each enrollment is plotted in **Figure 2**. A total of 242 patients were enrolled outside of business hours and 110 patients during business hours. The overall proportion of off-hour enrollments was 69% (95% CI, 62–75) as shown in **Figure 3**. When using only the trials that had a defined enrollment window (THICA, ACTS, THACA, and DKAT), the off-hour enrollment was 72% (95% CI, 66%–77%). When analyzed by day of the week, 255 patients (72.4%) were enrolled during weekdays and 97 patients (27.6%) enrolled during weekends. The enrollment pattern did not differ significantly across days of the week, ranging from 45 (12.8%) on Friday to 56 (15.9%) on Thursday as shown in **Figure 4*A***. When analyzed by time of day, enrollment from 2 PM to 10 PM accounted for more

TABLE 1.
Summary of Clinical Trials

Study	Study Period	Number of Participants (consented)	Enrolled Business Hours	Enrolled Off-Hours	Off-hours Enrollment	Enrollment Window	Enrolled in ED/ICU
THICA	2016–2022 (6 yr)	36 (45)	10	26	72.2%	12 hr from arrest	0/36
ACTS	2017–2019 (2 yr)	73 (85)	24	49	67.1%	24 hr	12/61
TRPSS	2018–2021 (3 yr)	70 (79)	30	40	57.1%	No set window	6/64
THACA	2018–2022 (4 yr)	76 (93)	21	55	72.4%	4.5 hr from arrest	49/27
DKAT	2018–current (6 yr)	97 (105)	24	73	80.4%	6 hr from last laboratory	74/23
Total	–	352 (407)	109	243	68.7%	–	141/211

ACTS = ascorbic acid, corticosteroids and thiamine in sepsis trial, DKAT = thiamine as adjunctive therapy for diabetic ketoacidosis, ED = emergency department, THACA = thiamine as a metabolic resuscitator in cardiac arrest, THICA = thiamine in cardiac arrest trial, TRPSS = thiamine for renal protection in septic shock.
Both ED and ICU enrollments were included in the analysis. Enrollment time used the time of signed consent for all studies other than THACA, which used the time of study medication administration. Business hours are defined as 9 AM to 5 PM Monday through Friday.

than 50% with the most frequent enrollment during 2–4 PM (51, 14.5%) and least frequently during 6–8 AM (7, 2.0%) as shown in **Figure 4*B***. Examining the enrollment progress for each trial showed that limiting recruitment to business hours only would have substantially increased the time required to reach the target number of patients, thus making the studies prohibitively long (**Fig. 5**; and **Fig. S1,** http://links.lww.com/CCX/B493). Note that for ACTS and TRPSS, which were multicenter studies, the horizontal dotted lines refer to the number of participants recruited at BIDMC only.

DISCUSSION

Effective study participant recruitment and enrollment is critical for the success and timely completion of clinical trials. Review of patient enrollment data from five critical care clinical trials clearly demonstrated that limiting patient recruitment to only business hours would have resulted in missing a significant number of potential study participants and in prohibitively longer study duration.

There has been limited research in this area. A 2008 survey of critical care practitioners and researchers by Cook et al rated after-hours and weekend enrollment to be some of the most important factors in successful recruitment (2). However, despite this, even in large academic centers, extended-hours recruitment is not common, as demonstrated by a study by Pattison et al (1) of critical care clinical trials in the United Kingdom that found that the typical work hours of research staff was around 8 hours per day with a few staffing 12 hours (7 AM–7 PM or 8 AM–8 PM). A 2013 multicenter cross-sectional study by the Canadian Critical Care Trials Group reviewing recruitment at 23 ICUs showed that ~25% of admissions occurred on weekends. Of 452 eligible cases, more than half of recruitment opportunities were missed and about 28% of them were due to lack of available research staff. Review of staff scheduling showed that research coordinators were available off-hours on weekdays around 56% of the time and on weekends 35% of the time (17). While this study was a multicenter study, the data was gathered over a very short duration (February 2009–June 2009) and the data are now more than 15 years old. A more recent systematic review of recruitment strategies for critical care trials showed that additional recruitment hours including evenings and weekends were associated with improved patient enrollment. Extended recruitment hours increased the number of healthcare proxies approached as much as 1.5 times

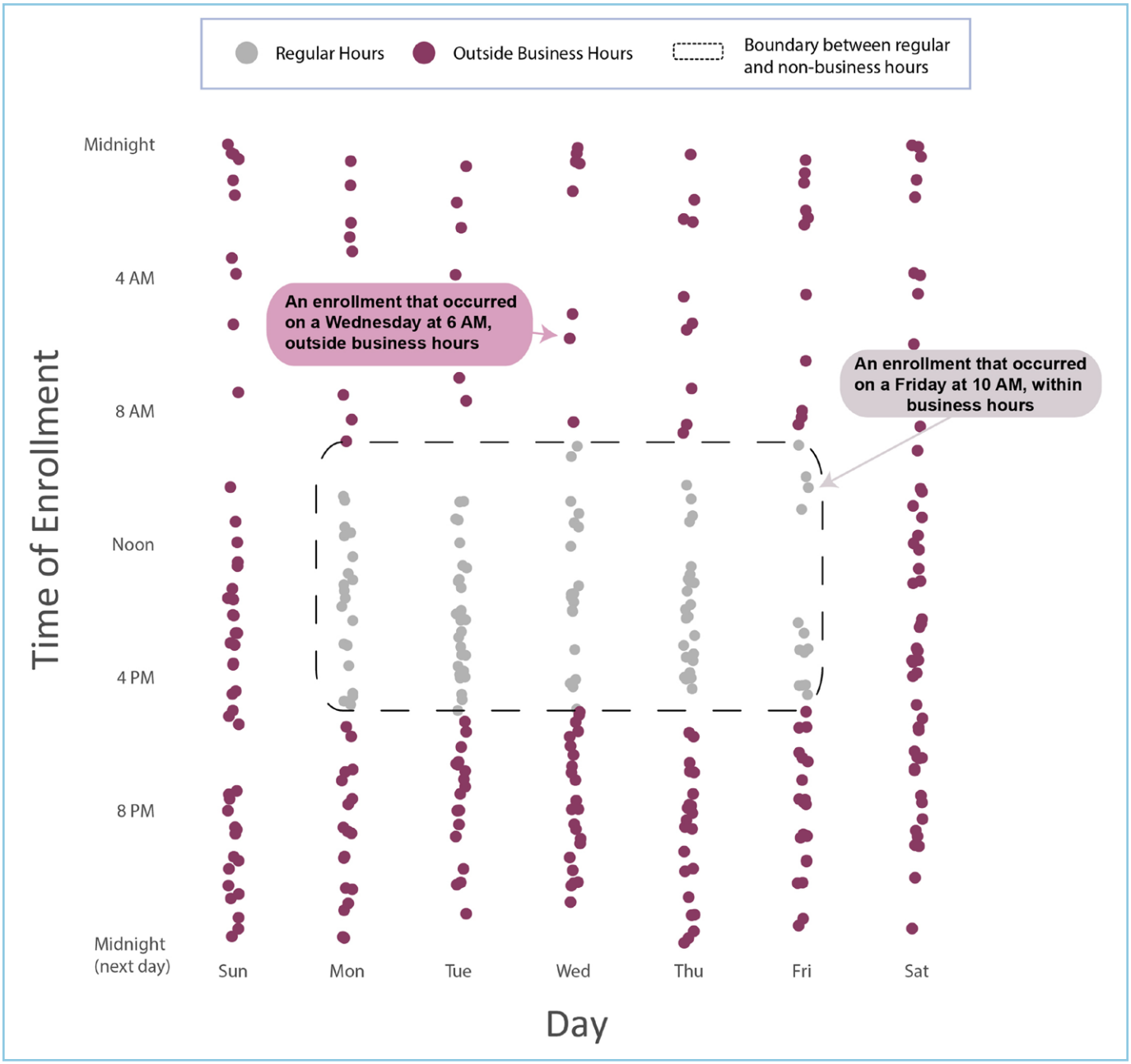

Figure 2. Enrollment timing over a week. Regular (business) hours are defined as 9 AM–5 PM Monday through Friday. Enrollment time used the time of signed consent for all studies other than thiamine as a metabolic resuscitator in cardiac arrest, which used the time of study medication administration.

more than day shift alone (9). In another study, adding a selective two-hour recruitment window seven days a week in the medical ICU was able to also increase patient enrollment (18). A study of recruitment in the PICU showed that extending recruitment to evenings and weekends allowed inclusion of family members who cannot present during working hours (19).

The trends observed in the enrollment data from our clinical trials are consistent with those reported in previous studies. However, we believe that our study is unique and an important addition to the relatively small body of work in this area because it provides an analysis of actual patient-level enrollment data from multiple critical care trials on several different target diseases over a relatively long period of time (2016–2024). Our analysis provides important data and evidence that extended-hours recruiting is not only helpful but necessary in some critical care trials. We believe that quantifying the degree to which extended-hour staffing affects recruitment provides a stronger

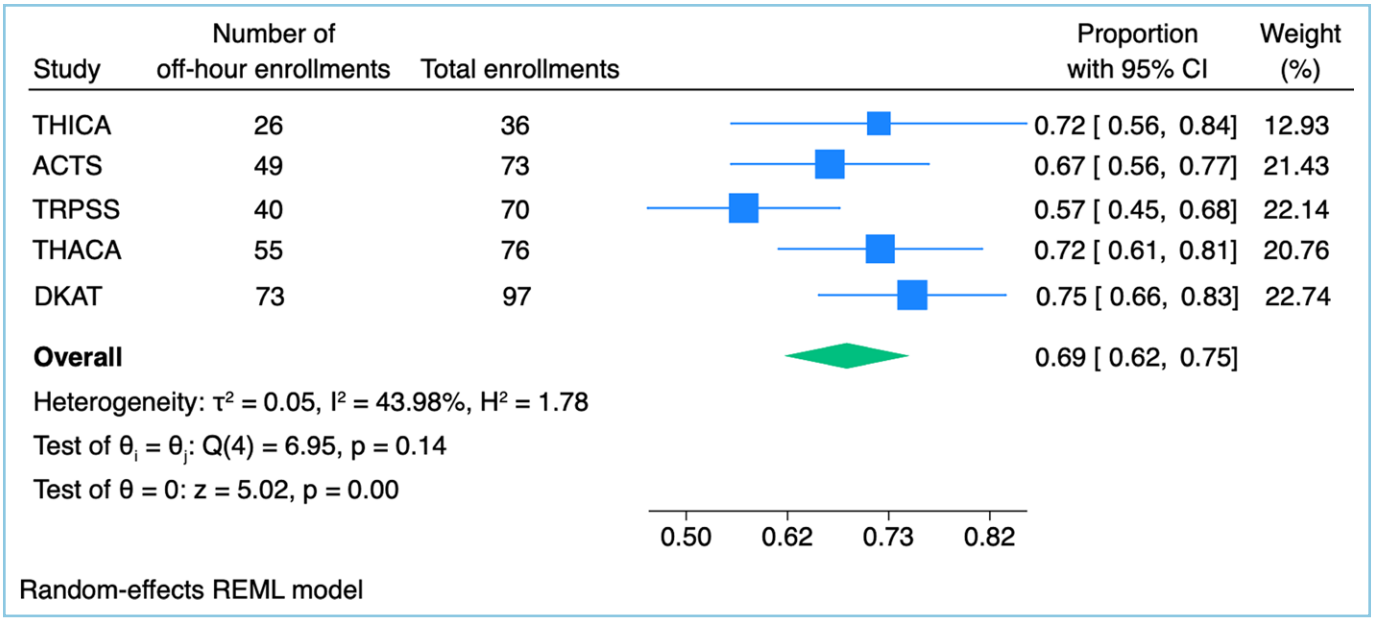

Figure 3. Forest plot of proportion of off-hour enrollments. Overall value was calculated using random-effect restricted maximum likelihood model. ACTS = ascorbic acid, corticosteroids and thiamine in sepsis trial, DKAT = thiamine as adjunctive therapy for diabetic ketoacidosis, THACA = thiamine as a metabolic resuscitator in cardiac arrest, THICA = thiamine in cardiac arrest trial, TRPSS = thiamine for renal protection in septic shock.

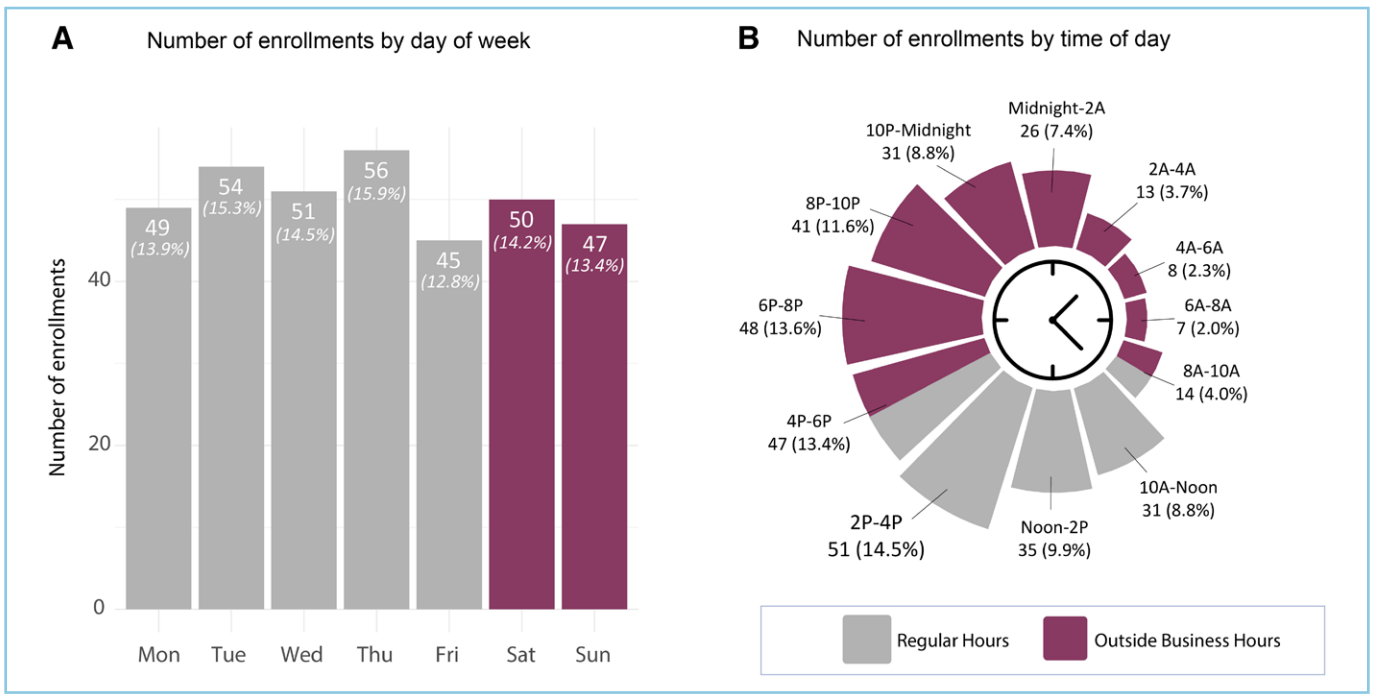

Figure 4. Analysis of enrollment pattern. **A**, Enrollment pattern across day of the week. **B**, Enrollment pattern across hours of the day. Regular (business) hours are defined as 9 AM to 5 PM.

and necessary basis for (1) consideration in budgeting, (2) hiring decision, (3) advocating for increased resources from the department/hospital, and (4) advocating for funding to the funding agencies. The data presented in this work provides concrete evidence for stakeholders to appreciate the magnitude of the impact of extended-hour recruitment or even more importantly, the drawback of not having extended-hour recruitment, and justify the allocation of additional resources. To our knowledge, this work is the first that provides patient-level data on recruitment on critical care studies spanning close to 10 years.

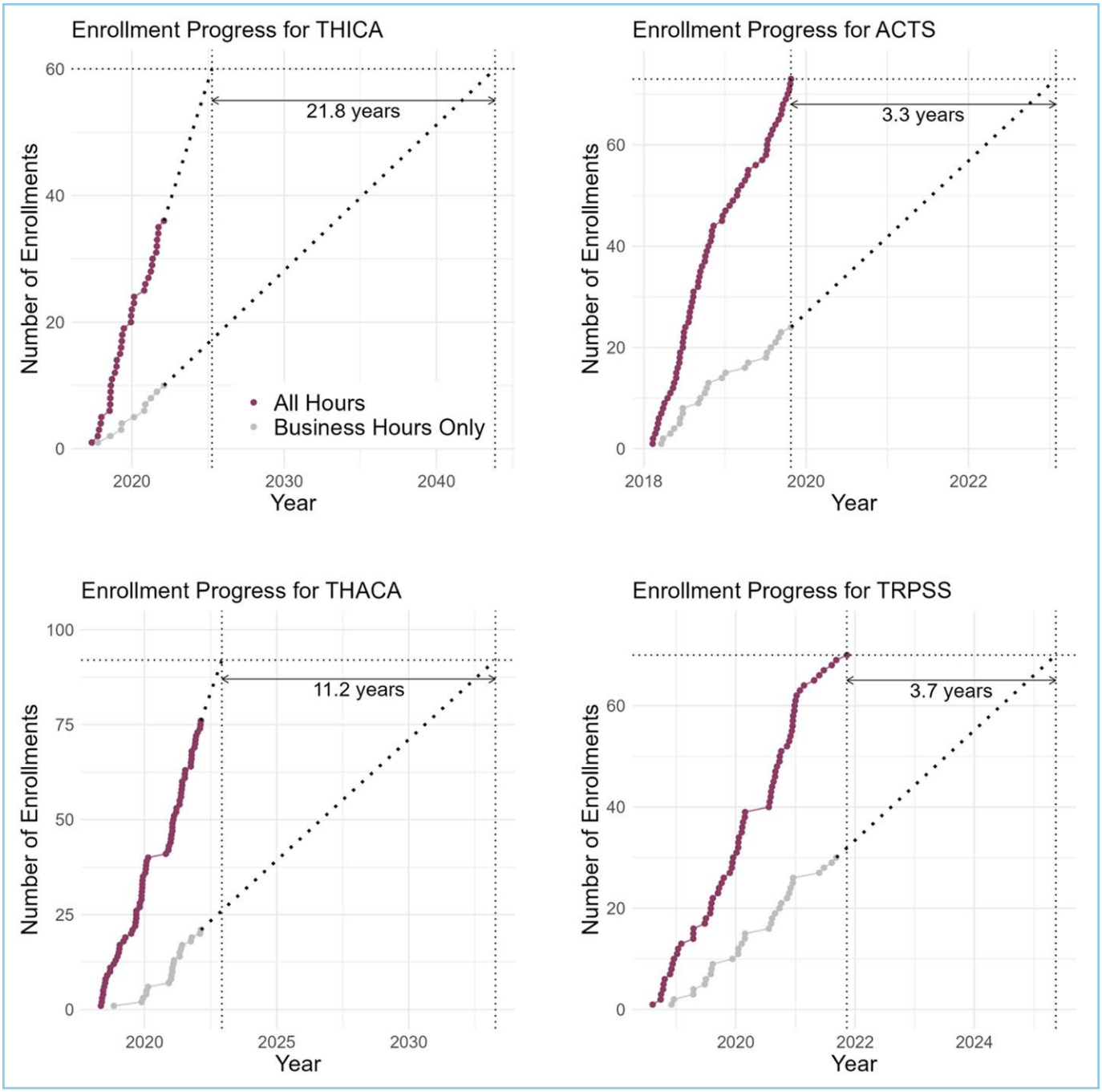

Figure 5. Enrollment progress for all thiamine in cardiac arrest trial, ascorbic acid, corticosteroids and thiamine in sepsis trial (ACTS), thiamine for renal protection in septic shock (TRPSS), and thiamine as a metabolic resuscitator in cardiac arrest trials. Purple line shows the enrollment progress using the extended-hours staffing strategy (24/7 enrollment). *Gray line* shows what the progress would have been if enrollment occurred during only business hours (9 AM to 5 PM). For ACTS and TRPSS, which are multicenter studies, the *horizontal dotted lines* refer to the number of participants recruited at Beth Israel Deaconess Medical Center only. THACA = thiamine as a metabolic resuscitator in cardiac arrest, THICA = thiamine in cardiac arrest trial.

Patient recruitment strategies must account for site-, study-, and patient-related factors. Site-related factors include available resources such as funding, number and capabilities of the research staff, and infrastructure (e.g., availability of research pharmacy). As described, our group has implemented 24/7 coverage by employing a three-shift structure, which includes overnight and weekend call shifts. In sites without sufficient resources to have dedicated research staff during off-hours, it may be necessary to have an investigator-led recruitment strategy where the principal investigator or co-investigators perform most,

if not all, of the recruitment tasks from screening to consenting. While this may be feasible in some settings, it would be challenging at our site as the study investigators are either ICU or ED attending physicians who cover multiple ICUs or the ED alone during off-hours. Given the clinical responsibilities, it is typically not possible for them to spend significant time on recruitment effort. Although investigator-led recruitment is better than not having any recruitment during off-hours, it is unlikely to serve as a comparable alternative to having dedicated research staff in large critical care studies where patient presentation is unpredictable and study interventions are often time-sensitive. While the specifics will vary depending on the research site, providing some degree of extended-hours recruitment, if 24/7 coverage is not feasible, may not only be helpful but also necessary for some studies depending on study-specific requirements.

An important study-related factor is the enrollment window, which typically depends on the specific condition and/or intervention being studied. For trials with a narrow enrollment window, the research staff typically needs to be available in person. In contrast, studies without such requirements may not need extended-hours coverage to the same degree. In our analysis, four out of five studies had specific enrollment windows, while one did not. Nevertheless, even for the studies without strict enrollment window, minimizing the delay between approaching the patient or LAR and enrollment is generally preferable to reduce the likelihood of clinical changes that may result in the patient falling out of the inclusion/exclusion criteria. In studies that require consenting the LAR, especially in pediatric studies, there are additional challenges such as the availability of parents or guardians at the bedside. This is an important factor that must be considered given that there may be substantial delay between approaching the LAR initially to consenting and finally enrolling, which leads to additional complexity to the recruitment process. This was demonstrated by a recent study by Armstrong et al in the PICU that showed that 35% of eligible patients did not have a LAR at the bedside on the first attempt and 23% of patients approached were not enrolled due to challenges associated with acquiring consent from the LAR (20).

Another important study-related factor is the condition being studied that may directly impact the enrollment rate. This is demonstrated in our analysis of cardiac arrest and sepsis trials. As shown in Figure 5, while limiting recruitment to business hours only would have dramatically prolonged the trial duration for both THICA and ACTS trials, the estimated additional time required to reach target sample size is significantly different (21.8 vs. 3.3 yr). While both are substantial extensions in time, the large difference in duration is largely due to the significantly lower incidence rate of in-hospital cardiac arrest (THICA) compared with septic shock (ACTS).

Last is the patient-related factor. This is not only pertinent in outpatient settings, but also in acute and critical care settings such as the ED where numerous studies have shown that the patient volume depends on the day of the week and time of day, often influenced by obligations outside of the patients' control such as work, childcare, etc (21, 22). For pediatric studies, the availability of parents and/or guardians for consent can be strongly impacted by these obligations. Notably, these challenges tend to impact those who have been previously underrepresented in research such as minorities and those with low socioeconomic status more. Therefore, recruitment strategy must consider these unique challenges to achieve a more diverse study participant population that is representative of the ultimate target patient population relevant to the study.

It may be helpful to consider several strategies. First, additional emphasis and consideration should be placed on budgeting for extended-hours recruitment during the initial planning phase of the study. We also believe that there should be an increased focus and support from funding agencies in this regard given that the common goal is to achieve well-performed and timely studies that may benefit the public. Second, many research sites may not have the capacity to offer full extended-hours coverage. A potential strategy is to adopt a data-driven approach by analyzing patient enrollment data early in the study to identify the most effective times to provide extend-hours coverage, which may allow improving recruitment in a more cost-effective manner. Another option, although may not apply to all studies, is the use of alternative consenting models such as deferred (or delayed) consent and EFIC, which may allow participants to be enrolled remotely during off-hours without requiring research staff to be physically present in the hospital. However, regulatory requirements governing research without prior consent (23) can vary significantly by site location (24). Lastly, engaging and training the research staff so

that they could lead and perform a substantial portion of the recruitment process may enable extended-hours coverage at reduced cost.

This study has several limitations. First, the trials analyzed in this study were single-center studies and therefore the result of the analysis may not be generalizable to other study locations. However, it is important to note that the research teams at large academic or tertiary hospitals where many critical care studies are conducted operate under similar conditions in terms of research infrastructure, staff scheduling, and challenges related to patient recruitment. Our institution is not fundamentally different from other major academic hospitals especially in the United States. Therefore, while generalizability is a limitation, the findings from our study are unlikely to be unique and likely applicable to similar settings. Also, while we reviewed over 350 patient enrollment data, the sample size is still relatively small.

CONCLUSIONS

In this study, we presented a research staff scheduling strategy to allow 24/7 patient recruitment for critical care studies. Review of our five recent critical care trials showed that nearly 70% of enrollment occurred outside of business hours. Limiting recruitment to only business hours would have resulted in a prohibitively longer time to complete the studies. This analysis provides a strong motivation and rationale for extending research staffing coverage beyond business hours.

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The data presented in this work are available from the corresponding author on reasonable request.

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