Enrolling Patients Into Clinical Trials Faster Using RealTime Recuiting™

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Abstract

Previous work has been done on both optimizing the clinical trials process, and on sending critical laboratory results and decision support through paging systems. We report the first integration of both these solution, focusing on improving the clinical trial recruitment process. We describe a clinical trial needing a real-time method of recruiting patients in an unbiased manner, quickly enough that study tests can be obtained before patients leave or samples discarded. The report describes how the ten currently recruited patients were found and how diagnoses of potentially life-threatening disorders are being made.

Background

Partly due to the needs of pharmaceutical companies and federal agencies, there have now been many projects that have been developed in an academic setting attempting to optimize various parts of the clinical trial process. Ohno-Machado, et al., developed software to determine clinical-trial eligibility for patients with breast cancer. Each clinical trial criterion was translated into Arden syntax, and the entire protocol was represented using XML. [1] The system is designed to be used by a physician, and takes patient characteristics and outputs clinical trials for which the patient is eligble. Similarly, Rubin, et al., designed a Java-based system to author and store eligibility criteria for patient enrollment [2], and Tu and Musen developed a schema for storing clinical guidelines. [3] Silva and Wittes previously described how the National Cancer Institute is developing the web-based Cancer Informatics Infrastructure, to reduce physician administrative burden required to enroll patients. [4]

Many of these projects have documented a few clinical trials that have benefitted from these software services; however, very few of these projects document an actual increased number of enrolled patients. The enrollment process itself involves a complicated decision on the part of the health-care provider, which includes: [5]

- Remembering active protocols for a condition
- Explaining trials to patients
- Having time to perform the recruitment

One may argue that clinical trial enrollment should be performed by those most familiar and interested in the study. To this end, and to date, there have been no systems designed that specifically find patients that qualify for clinical trials, so that study coordinators can enroll those patients. In addition, this has not been done in a real-time manner.

Real-time messaging and paging systems have been used in a number of clinical settings for more than a decade. Kuperman, Teich, Safran, and others have experimented with and described systems in their hospitals where clinicians are notified of critical laboratory results. [6-8] These are considered standard of care in some settings. Wagner, et al., described how house staff prefer certain communications channels (e-mail or pager) for certain types of messages. [9]

More recently, Wilbright, et al., demonstrated how a paging system can be used to send important facts from recent medical publications to house staff. [10] Miller, et al., showed how clinical alerts can be generated by pharmacy systems and sent via pager to responsible providers. [11] Tsui, et al., provided a web-based system where house staff could customize alert preferences via a web interface, but found it to be poorly used in their setting. [12]

None of these messaging systems are particularly focused on the specific problem of recruiting patients into clinical trials.

Finding Patients in Real-time

In collaboration with the Division of Endocrinology at our hospital, we discovered a requirement for information services for a specific clinical study. This clinical research project had four particular needs that made conventional methods of patient recruitment unusable. First, previous work showed that there were only a few potential patients that would fit the

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entry criteria, on the order of one or two per week. Second, the study was to take place in the emergency department of a large tertiary care hospital, where many staff and trainees rotate on a weekly basis servicing approximately 50,000 encounters yearly. Thus, it would have been difficult to teach every single provider about the study.

Third, this research project needed patient samples to be collected in the emergency department setting before the patients were treated. Samples collected after treatment would not have been as sensitive for this study.

Fourth, previous competitive research projects in this field were complicated by recruitment patterns. These previous projects had been criticized because only patients with severe presentations were recruited, thus potentially biasing their results.

Our purpose was to design a system that would find patients qualifying for this clinical research project, allowing these four requirements to be filled.

Methods

Incidentally Found Hypoglycemia

A retrospective study by Weinstein, et al., showed that pediatric patients sometimes have hypoglycemia (low blood sugar) when they present to an emergency department with common complaints, including gastroenteritis, viral syndromes, and dehydration. [13] Although non-intuitive, his work demonstrated that most pediatric patients do not present with hypoglycemia, even when they have severe dehydration. This suggested that hypoglycemia is actually a rare event in the emergency department setting, and deserves special consideration. The retrospective work showed that the patients with hypoglycemia were likely to be found to have a previously undiagnosed endocrinologic or congenital metabolic disorder, *when the proper diagnostic tests were sent*. Some of these endocrinologic and metabolic disorders are associated with repeated hypoglycemic events, and some are associated with sudden death.

However, the majority of the patients with hypoglycemia in the retrospective study did not have the proper studies sent. At the time, sending these special diagnostic laboratory tests was optional, and not considered as the proper clinical standard of care.

Prospective Clinical Trial

The decision was made to proceed to a prospective clinical trial to study the outcomes of pediatric patients presenting with hypoglycemia. However, as described above, the nature of this clinical trial was complicated. The special diagnostic tests, including serum and urine organic acids, were most sensitive when run on specimens collected before glucose was given. These urine specimens were often obtained, and excess was typically discarded. However, withholding glucose from patients with hypoglycemia is, at the very least, unethical, and at worst, life threatening. Thus, these potential enrollees needed to be found in real-time, and the treating clinicians needed to be notified immediately to save the specimens.

Existing Infrastructure

Our emergency department has a specific application to manage the registration process. Data in this application is tied to the hospital's Oracle central repository, as shown in the figure. Laboratory test results are automatically entered using Cerner systems, and are transferred into the same centralized Oracle repository.

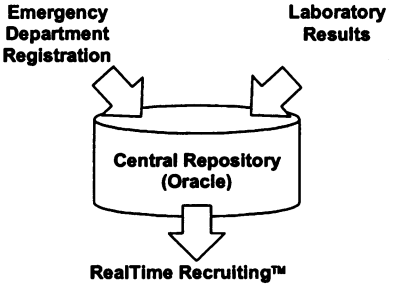

Figure: Schematic of information flow

Software

We created a software program that scans all patients in the emergency department at a fixed frequency (every 2 minutes). The software uses a query looking at the time patients were registered.

All blood sugars for patients registered in the emergency department are scanned, and any patient with a blood sugar under 50 mg/dl (2.8 mmol/L) is flagged. For these patients, a text message is constructed concatenating patient identifiers, the laboratory test and result, and the time and date of the test. This message is then sent via pager to the study coordinator 24 hours a day; specifically, pages are sent by automatically filling out and submitting a web-based form. The study coordinator then calls the emergency department to speak with the clinician and determines the clinical condition of the patient. Since

Patient	Age	Blood Sugar (mg/dl)	Presentation	Course and Diagnosis	Pre-treatment samples obtained
1	9 months	38	Seizure	Diagnosed with excessive amounts of insulin secretion.	Yes
2	16 months	38	Vomiting	Admitted; team unaware of hypoglycemia in emergency department. Workup for inborn error of metabolism abnormal, pending.	No
3	17 months	32	Vomiting and diarrhea	Has inborn error of metabolism. Since presentation, has had four episodes of recurrent hypoglycemia.	Yes
4	17 months	40	Vomiting and decreased intake	Has inborn error of metabolism; final diagnosis pending.	Yes
5	27 months	44	Vomiting and diarrhea	Work-up pending.	Yes
6	3 years	21	Lethargy	Diagnosed with congenital insufficiency of adrenal glands.	Yes
7	11 months	48	Vomiting and diarrhea	Sent home before glucose result available. Tests added to specimens already collected. Diagnosed with excessive amounts of insulin secretion.	Yes
8	13 months	49	Vomiting and diarrhea	Work-up pending.	Yes
9	33 months	47	Vomiting and diarrhea and decreased intake	Work-up pending.	Yes
10	32 months	49	Vomiting and diarrhea and decreased intake	Work-up pending.	Yes

Table: Patients enrolled in the emergency department hypoglycemia study to date. Each patient was discovered using the RealTime Recruiting™ software system. Inclusion criteria includes glucose under 50 mg/dl and no previous diagnosis that would cause hypoglycemia. Although we cannot be absolutely certain, we presume none of these patients would have been recruited for this study without the prompts from this software system.

this study was focused on finding patients who are currently undiagnosed, one exclusion criteria for the study was that patients must not have had a previous diagnosis that might explain the hypoglycemia.

The study coordinator then speaks with the parents of the patient and if consent is obtained, enrolls the patient. The coordinator then arranges for the specific laboratory tests to the performed on any specimens that have not been discarded, or directs the emergency department to obtain more specimens.

The study coordinator can view a specific web-site that shows a deidentified list of patients and blood sugars from the past 24 hours, and a list of the pages sent.

The RealTime Recruiting™ software was written in Java and database connections are made using JDBC. The software was written as a Java servlet that

spawns an autonomous thread performing the frequent database polling. The software runs under JRun and IIS in Windows NT.

Results

At the time of writing, the study has been running for four months. During the four months; a total of 13 pages were sent. Of these, 11 patients met the other inclusion criteria for the study (having no previous medical problems that would explain hypoglycemia). Parents for ten patients were given informed consent and all ten were recruited and are listed in the table. The eleventh patient was in critical condition and was admitted to a newborn intensive care unit. Since, by definition, we are capturing all patients with hypoglycemia in the emergency department setting, the sensitivity of this system is 100%. Since three of the thirteen patients were not recruited, the specificity of the system is 77%. Clearly, for finding a rare disorder like hypoglycemia, these are desirable sensivity and specificity.

The ten patients were recruited based solely on the active initiation of the study coordinator, as prompted by the paging system; in other words, the contacted emegency department provider had not been considering this research study. Nine of the ten patients had pre-treatment samples that were able to be sent for comprehensive testing. This was important, since it is more dififcult to diagnose certain disorders like excessive insulin and inborn errors of metabolism using specimens obtained after glucose correction Although final diagnoses are pending on most patients, several of the patients have abnormalities detectable on metabolic testing. All of the disorders found or under consideration are associated with seizures or suden death.

Patient Anecdotes

Patient 6 presented with difficulty arousing, but had had this type of symptom before without diagnosis. In fact, this patient's primary physician discouraged full diagnostic testing. Early testing showed a deficiency in cortisol and further testing showed an increase in ACTH and negative anti-adrenal antibodies, all consistent with a adrenal hypoplasia congenita.

Patient 7 presented with vomiting and diarrhea. Point-of-care glucose testing showed hypoglycemia, and the patient was treated with IV glucose and discharged to home. Samples sent to the laboratory confirmed the low blood sugar and the study coordinator was automatically paged. All collected specimens were then immediately saved and sent for diagnostic testing, which later showed excessive production of insulin and hypoketonuria.

Discussion

This is the first reported use of a real-time messaging system to recruit patients for a clinical research study. To date, this system was able to find patients for recruitment that would have otherwise been missed. In this way, unbiased patient recruitment can occur which has the benefit of maximizing patient enrollment. In addition, the system notifies study personnel fast enough that specimens can be sent for testing before they are discarded.

Six issues arose during the construction of this system. First, the hospital's institutional review board approved this clinical study, so that charts of emergency department patients could be reviewed for hypoglycemia. We had to approximate this process within the software system. Only laboratory results on current or recently enrolled emergency department patients are scanned. Setting up a trigger in the laboratory computer or scanning all patients in the hospital system would have exceeded the terms of the approval.

The second issue dealt with the timing of laboratory tests. Occasionally, a specimen might be sent for glucose testing before the patient is enrolled; this might occur when a critically ill patient arrives and registration information cannot be collected. Similarly, triage nurses with standing orders may place intravenous lines and send labs before full registration is completed. This software system solves this problem by looking for specimens that may have been sent up to an hour before patients were registered.

The third issue is the opposite problem. Due to occasional delays, laboratory testing may not be performed, or results may not arrive for several hours. This system scans for labs of patients who are either currently registered in the emergency department, or who were registered up to eight hours prior. Thus, laboratory results that return within eight hours of registration will be found.

Security is a concern within such a system. A paging system is not point-to-point secure, and may be intercepted. Sending minimal patient identifiers would be ideal; however, the receiving study coordinator needs enough information to quickly determine the correct patient and find the treating provider. Currently, the name and patient identifier is

sent over the paging system. In the future, we could modify the system to send a URL, so that the study coordinator could connect using SSL and password authentication to get the particulars.

Occasionally, the central repository is taken offline for backups or upgrades. When the system detects a fault in the connection, it sends pages with error conditions to the system administrator (not the study coordinator). The administrator can then determine whether the error represents a temporary or permanent condition, and can then fix any problems as needed.

The sixth issue deals with polling the database. Queries needed to be constructed to use indexed fields; otherwise the frequent polling might theoretically constitute a burden on the database system.

Future Directions

Although this software integrates systems in a uncomplicated manner, it does so for a unique purpose in a novel way. The system is already being adapted for two additional emergency department studies, and will be part of a core facility at our hospital for many other studies.

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