Using real-time alerts for clinical trials

Identifying potential study subjects

E. Chow[1]; M. Zuberi[2,3]; R. Seto[2]; S. Hota[6,7]; E.N. Fish[8,9]; D. Morra[1,4,5]

[1] Centre for Innovation in Complex Care, University Health Network;
[2] Investigational Pharmacy Services, Department of Pharmacy Services, University Health Network;
[3] Leslie Dan Faculty of Pharmacy, University of Toronto;
[4] Department of Medicine, University of Toronto;
[5] Centre for Interprofessional Education, University of Toronto;
[6] Department of Infection Prevention and Control, University Health Network;
[7] Division of Infectious Diseases, Department of Medicine, University Health Network;
[8] Toronto General Research Institute, University Health Network;
[9] Department of Immunology, University of Toronto

Keywords

Alerting, clinical trials recruitment, clinical trials conduct, handheld devices, messaging

Summary

Background: Clinical trials are widely accepted as a necessary step in evaluating the safety and efficacy of new pharmaceutical products. In order for a sufficiently powered study, a clinical trial depends on the effective and unbiased recruitment of eligible patients. Trials involving seasonal diseases like influenza pose additional challenges.
Objective: This is a feasibility study of a mobile real-time alerting system to systematically identify potential study subjects for a randomized controlled trial evaluating the safety and efficacy of early intervention with interferon alfacon-1 for patients hospitalized for influenza virus infection.
Methods: The alerting system was setup in a 471-bed acute care teaching hospital, enabled with computerized physician order entry (CPOE) and a rules-based alerting system. Patients were identified from the entire hospital using two alerts types: pharmacy prescription records for antiviral drugs, and positive influenza laboratory results. Email alerts were generated and sent to BlackBerry® devices carried by the study personnel for a 6 month period. The alerts were archived automatically on a secure server and were exported for analysis in Microsoft Access.
Results: Over a period of 21 weeks, 779 total alerts were received. The study team was alerted to 241 patients, of whom 85 were potential study subjects. The alert system identified all but one of the patients independently identified by infection control.
Conclusions: Real-time identification of potential study subjects is possible with the integration of computerized physician order entry and BlackBerry® technology. It is a viable method for the systematic identification of patients throughout a hospital, particularly for trials investigating time-sensitive disease progression.

Correspondence to:
Dante Morra, MD MBA FRCP(C)
Centre for Innovation in Complex Care,
University Health Network
Toronto General Hospital
200 Elizabeth Street
Eaton North 14–209A
Toronto, Ontario
Canada, M5G 2C4
E-mail: Dante.morra@uhn.on.ca

1. Introduction

Clinical trials are widely accepted as a necessary step in evaluating the safety and efficacy of new pharmaceutical products. In order for a sufficiently powered study, a clinical trial depends on the effective and unbiased recruitment of eligible patients [1, 2]. Recruitment however, is recognized as a challenge [3–7] and the demands placed on the team present a significant barrier that should be minimized [6].

Trials involving seasonal diseases like influenza pose additional challenges. Patients infected with influenza may be located throughout the hospital with varying degrees of acuity in the emergency department, internal medicine or in intensive care. Limited personnel for a study make recruitment difficult, given the geographic distribution of these care settings. Moreover, the need for immediate therapy [8] and the rapid presentation of influenza introduces a very short window for recruitment, as eligibility may be limited to within several days of symptom onset. Viewed together with the seasonal nature of influenza, where eligible patients arrive in waves [9, 10], this necessitates that a high number of patients be recruited in a short period of time.

Computerized real-time recruitment of eligible patients has been reported as a method to improve study investigator notification [3, 7, 11] and has been associated with increased referrals and enrollment [12]. Such an application was found to improve investigator notification from 56% to 84% in the emergency department [3]. In this case report, the authors present a feasibility study of a similar, but more mobile application, a BlackBerry® enabled real-time alerting system to improve the identification of potential study subjects for a randomized controlled trial evaluating the safety and efficacy of early intervention with interferon alfacon-1 for patients hospitalized for influenza virus infection. Potential study subjects for this clinical trial are those who have been identified to have probable or confirmed influenza infection but require further screening to determine eligibility.

Mobile platforms have been used in attempts to improve communication between clinicians [13, 14] and physician perceptions towards smartphones are positive in comparison to conventional paging methods [14]. The study team adopted a mobile platform to allow for immediate alerting without being geographically restricted to ward-specific recruitment.

2. Methods

The Toronto General Hospital is a 471-bed acute-care teaching hospital equipped with an electronic patient record that includes Computerized Physician Order Entry (CPOE), and diagnostic test reporting. Patients with influenza virus infection normally present in the emergency department, but may also present in other wards where they may be admitted for other reasons, including respirology, internal medicine or the intensive care unit. These patients are seen by a physician who orders the appropriate diagnostic tests and treatment through CPOE.

The eligibility criteria for the clinical trial included confirmed influenza virus infection, age 18 to 70 years, symptom onset of less than eight days and inpatient admission. Potential study participants were identified by abnormal laboratory results reported in CPOE or by antiviral treatment ordered by the physician, also in CPOE. The principal investigator evaluated the exclusion criteria and determined the final eligibility to the clinical trial after consent obtained from the patient.

A number of communication strategies were used to promote patient recruitment throughout the institution. It was not feasible to have a study team member at each ward and so a series of presentations were conducted and information pamphlets were distributed to inform staff of the clinical trial. A dummy enrolment run-in phase [15] was conducted in the month prior to initiation, to ensure appropriate enrollment without the violation of key inclusion criteria.

Recruitment using the BlackBerry® enabled real-time alerting system occurred over 6 months from October to March, excluding the holiday period from December 14th, 2010 to January 3rd, 2011 and all weekends. Personnel on the study team, including the principal investigator, study coordinators and research pharmacist were provided with BlackBerry® smartphones connected to a secure and private network. On these devices, they would receive two alert types generated as emails by Misys Insight (Misys Healthcare Systems, Raleigh NC), an alert-building software that interfaces

with CPOE. The first were prescription orders of oseltamivir, zanamivir, and amantadine, which are antiviral drugs prescribed for treating influenza virus infection; the second were laboratory requests or results for influenza virus testing, including nasopharyngeal swabs, throat swabs, sputum, endotracheal tube aspirate, or broncho-alveolar lavage. The alerts were programmed by the study pharmacist in consultation with the Misys support group.

Infection control records of positive test results for influenza virus, or patients under isolation precaution for influenza-like illness, were available to the study team. However, the time delay associated with the receipt of these reports made them impractical for use in recruitment. When an alert was received, a member of the study team would consult with the patient's physician before obtaining consent and screening for eligibility (▶Fig. 1).

All email alerts generated were automatically archived on a secure email server independent from the BlackBerry® devices. The archived emails were exported to comma-delimited format for analysis with Microsoft Access. Structured Query Language (SQL) queries were written to calculate: i) the total number of alerts received for antiviral prescriptions and positive laboratory results; ii) the total number of potential study subjects identified by the BlackBerry® enabled real-time alerting system compared to the total number of potential study subjects identified by historical Infection Control records; and iii) the frequency of first-alerts. These measures provide an assessment of how comprehensively potential study subjects can be identified as well as the effort placed on the study team to investigate the alerts. Each potential study subject has a unique first-alert; the first alert to be received by the study team whether for an antiviral prescription or a positive laboratory result is considered the first alert for that potential study subject.

The historical Infection Control records were reported independent of the data collection for this study and were received several weeks after the data collection period, to validate the BlackBerry® system.

3. Results

Over the recruitment period, the study team was alerted to 241 patients by the BlackBerry® enabled alerting system through antiviral prescription alerts and positive laboratory alerts as shown in ▶Table 1. These patients were admitted throughout the hospital in internal medicine, critical care, transplantation, general surgery, intensive care, cardiology, gynecology and respirology. Only 85 of the 241 alerted patients were infected with influenza virus and were potential study subjects. After obtaining consent and screening, none of the potential study subjects were enrolled to the study due to age limitations or other medical complications. Infection control records had identified that 83 patients had confirmed influenza virus infection during the same period. Infection control records identified one patient that our system did not report. Compared to infection control records, our alerting system identified nearly 99% of patients with confirmed influenza virus infection and identified an additional two patients that were not reported in Infection Control records.

The study team assessed 779 alerts in total. Only 535 of the alerts were for potential study subjects, and since only the first alert is the most relevant for initial identification, only 85 alerts were relevant for identifying potential study subjects. Subsequent alerts for an already identified patient resulted from multiple order entries in the CPOE by the physician.

The first alerts for all patients identified by the BlackBerry®-enabled real-time alerting system are shown in ▶Figure 2. Alerts were received through the day with apparent peaks in the morning and afternoon. When the alert frequency is considered on a weekly basis, a 'wave' of influenza patients was apparent, starting in early December as seen in ▶Figure 3.

4. Discussion

The study team was able to manage a hospital-wide recruitment strategy by implementing a BlackBerry® enabled real-time alerting system. The alerts provided a systematic approach to identifying potential study subjects without a geographic selection bias.

Weiner et al. report an improvement from 56% to 84% identification of potentially eligible patients with an automated system [3, 16]. Our BlackBerry® enabled real-time alerting system allowed the identification of 99% of potential study subjects, who were also identified by Infection Control. Factors that contribute to the high identification rate of our system include: the inclusion criteria of the clinical trial, and the sensitivity of programmed alerts. The clinical trial in this study had very clearly defined inclusion criteria for positive influenza virus infection. These criteria have little ambiguity, are comprehensively documented in the CPOE and are readily programmable as alerts. Other clinical trials may have different identification rates depending on these factors.

4.1 Strengths and weakness of intervention

On average, each potential study subject generated 6.3 alerts. The redundant alerts occur for repeated reports of laboratory results for viral determination or for each antiviral drug order entered by a physician. Both events were selected, to ensure the rapid initial identification of patients who may have been eligible. Selecting the events to be alerted for is a balance between timely alerts and comprehensive identification with implications to effort for the study team. A limitation of this study is the lack of formal evaluation of the perceptions of the alerting system with the study team and healthcare providers; informal discussions with physicians participating in the study suggest positive perceptions from the reduced need to be constantly aware of the study criteria [17].

Alert redundancy could be reduced by implementing further conditions in the programmed alerts. Subsequent alerts for patients who have already been identified as potential study subjects could be filtered to reduce false alerts. This limitation was also reported by the experience of other authors [3].

Other events of potential study subject identification could be explored for more rapid initial identification. For example, isolation precaution orders may occur prior to both antiviral drug orders or laboratory results. Unfortunately, isolation precautions are not specific to influenza virus infection and may increase the number of false alerts for studies specific to influenza only.

The clinical trials alerting system we describe is only possible in settings with an electronic medical record and CPOE integration. The dependence on EMR and the compatibility of the Misys alerting system with the EMR may be a limitation of this application.

4.2 Significance and Application

A clinical trial alert system was used in an outpatient settings to improve referrals and enrollment [12] and the results from our observations suggest similar improvements are possible for an in-patient setting. A real-time clinical trial alerting system is widely applicable as it may allow for the efficient identification of potential study subjects for multiple studies [18]. Such a system could be scaled to consider other routinely collected data in the EMR [19]. This would be particularly useful for clinical trials involving patients who present to many hospital wards, or for clinical trials that require a rapid initiation of study interventions and timely sample collection.

A clinical trials alert system may be well suited for intensive care settings, where complex considerations are needed for the recruitment of critically ill patients to multiple available clinical trials. The use of a non-electronic screening log has been used for recruitment into multiple trials in the intensive care unit [20]. A clinical trials alert system may assist in managing the complexity of co-enrollment to multiple clinical trials in the ICU, a practice that some clinicians are endorsing [21].

Another benefit would be to better understand when potential study subjects become eligible for enrollment. By receiving alerts in real-time, it is possible to anticipate future peaks and valleys [10] in recruitment, allowing for a more directed use of study team resources.

Using real-time alerts would also be quite valuable outside of clinical research. For example, patients eligible for prophylaxis or treatment of a condition could be proactively identified. By using BlackBerry® smartphones, pertinent information can reach the team responsible for the patient in real-time, thus allowing for instant communication and appropriate action. Similarly, real-time alerts may have valuable application in hospital epidemiology in alerting providers of the need for increased precautionary measures.

5. Conclusion

Real-time identification of potential study subjects is possible with the integration of CPOE and BlackBerry® technology. It is a viable method for ensuring the comprehensive and systematic identification of patients to approach for consent and enrollment to trials investigating time-sensitive disease progression. Further research in the development of automated alerting for the clinical-trial recruitment process is warranted.

The use of automated alerting is applicable both in the context of subject recruitment for clinical trials, and also in the context of infection control and management. The further development of alert logic sets, and the integration of these automated identification tools with CPOE may provide a more efficient use of resources in response to seasonal waves of influenza infection.
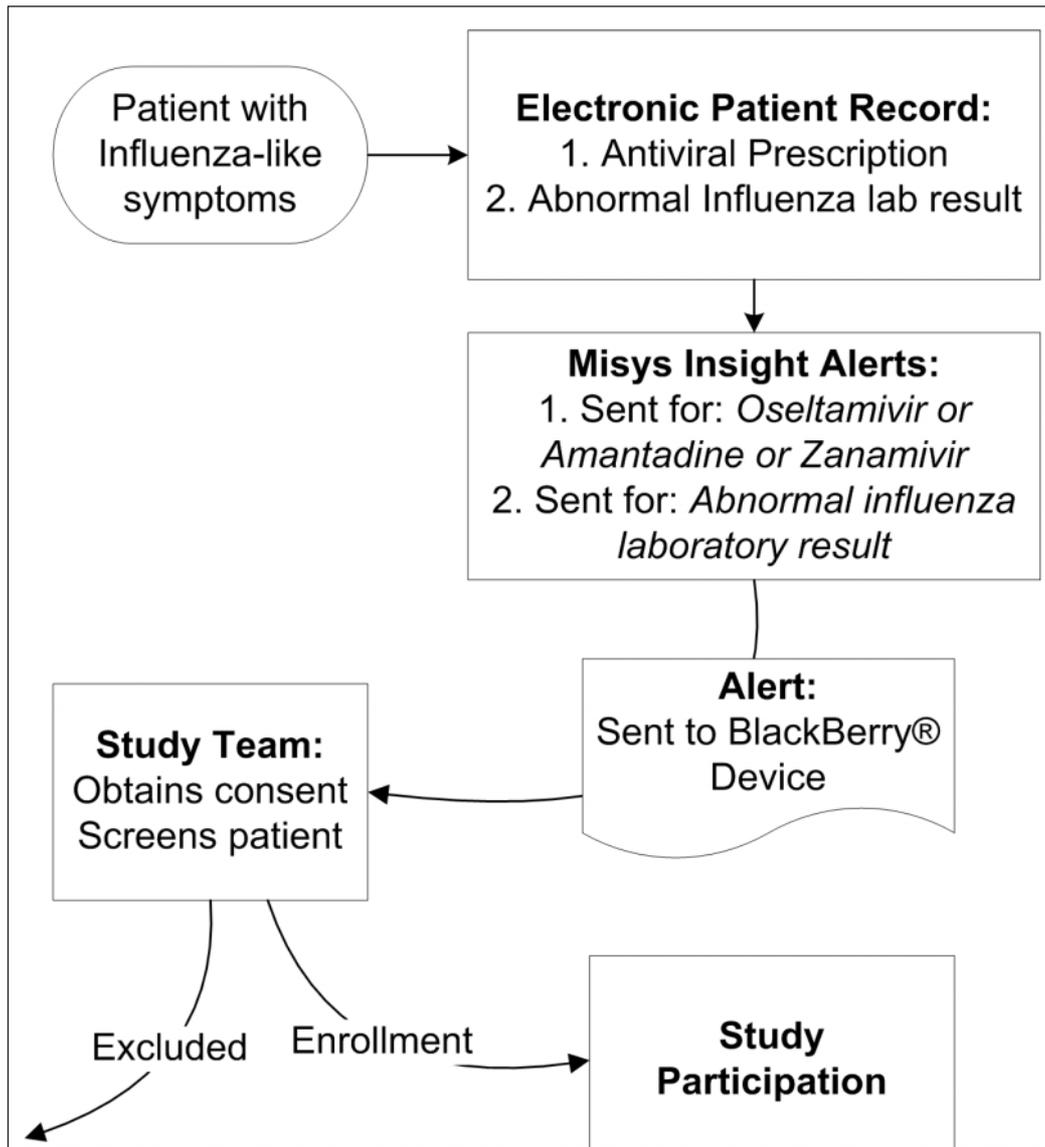
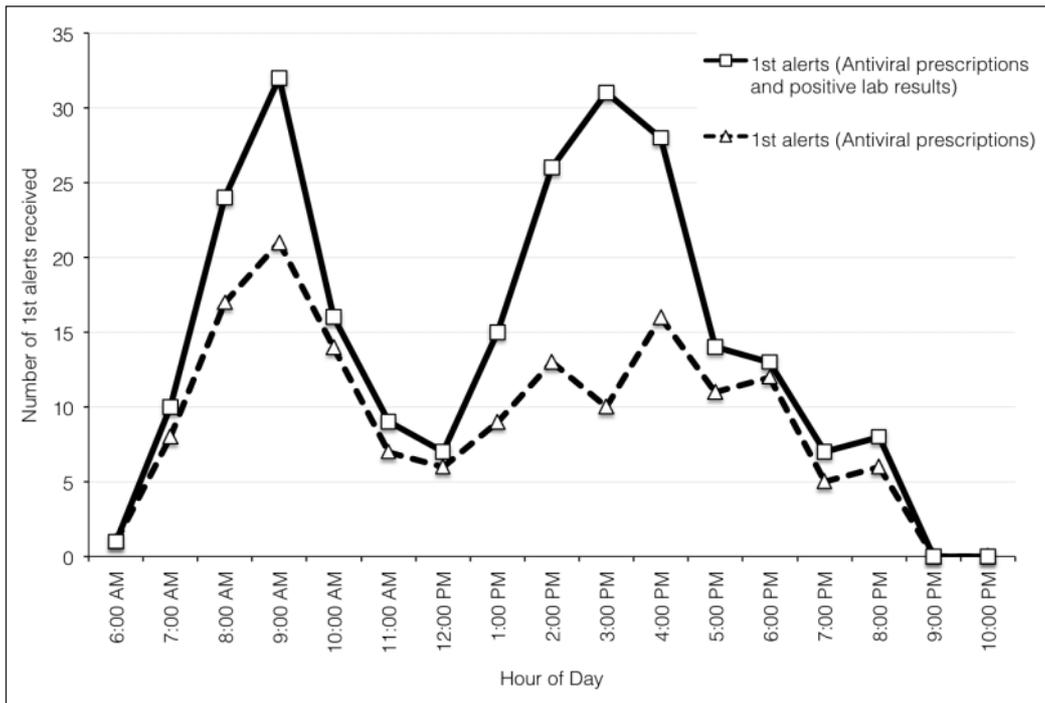**Fig. 1** Process of potential study subject identification

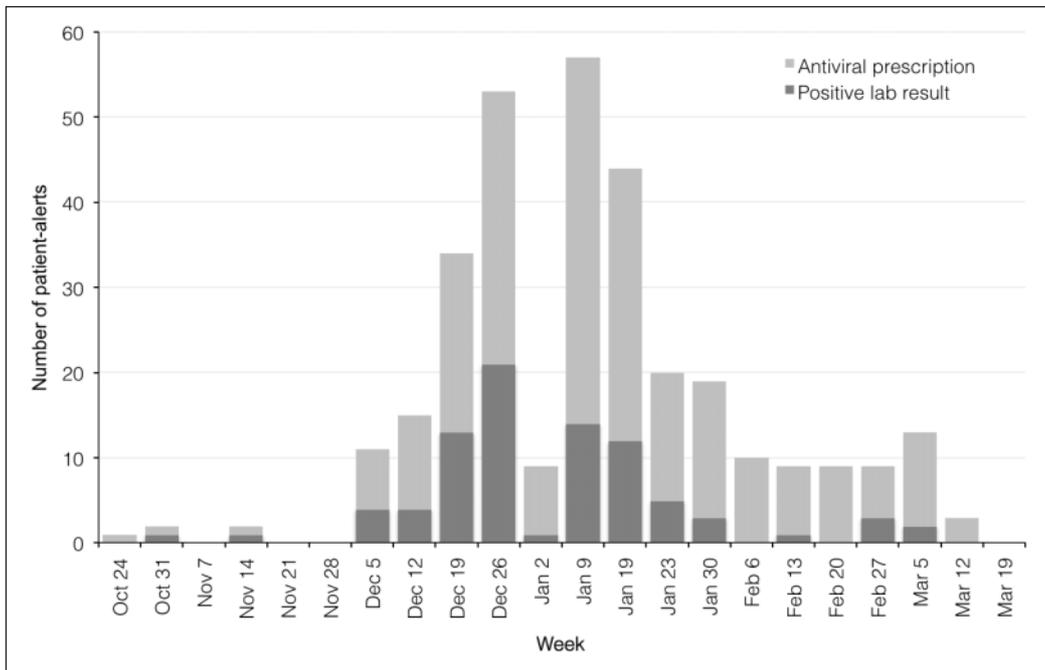**Fig. 2** First alert frequency by time of day (all patients)

Fig. 3 First alert frequency by week (all patients)

Table 1 Alerts received using a BlackBerry® enabled real-time alerting system. Potential study subjects for this clinical trial are those who have been identified to have probable or confirmed influenza infection but require further screening to determine eligibility. The first alert to be received by the study team whether for an antiviral prescription or a positive laboratory result is considered the first alert for that potential study subject.

	Potential Study Subjects	False Alerts	All Patients
Number of Patients	85 patients	156 patients	241 patients
positive Influenza Alerts (first alerts)	401 (45)	0 (0)	401 (45)
Antiviral Prescription Alerts (first alerts)	134 (40)	244 (156)	378 (196)
Total Alerts	535	244	779

References

1. Crowley ST, Chertow GM, Vitale J, O'Connor T, Zhang J, Schein RM, et al. Lessons for successful study enrollment from the Veterans Affairs/National Institutes of Health Acute Renal Failure Trial Network Study. Clin J Am Soc Nephrol 2008; 3(4): 955–961.
2. Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, et al. Factors that limit the quality, number and progress of randomised controlled trials. Health Technol Assess 1999; 3(20): 1–143.
3. Weiner DL, Buttle AJ, Hibberd PL, Fleisher GR. Computerized recruiting for clinical trials in real time. Ann Emerg Med 2003; 41(2): 242–246.
4. Campbell MK, Snowdon C, Francis D, Elbourne D, McDonald AM, Knight R, et al. Recruitment to randomised trials: strategies for trial enrollment and participation study. The STEPS study. Health Technol Assess 2007; 11(48): iii, ix-105.
5. Caldwell PH, Hamilton S, Tan A, Craig JC. Strategies for increasing recruitment to randomised controlled trials: systematic review. PLoS Med 2010; 7(11): e1000368.
6. Ross S, Grant A, Counsell C, Gillespie W, Russell I, Prescott R. Barriers to participation in randomised controlled trials: a systematic review. J Clin Epidemiol 1999; 52(12): 1143–1156.
7. Afrin LB, Oates JC, Boyd CK, Daniels MS. Leveraging of open EMR architecture for clinical trial accrual. AMIA Annu Symp Proc 2003: 16–20.
8. Kumar A. Early versus late oseltamivir treatment in severely ill patients with 2009 pandemic influenza A (H1N1): Speed is life. J of Antimicrobial Chemotherapy 2011; 66: 959–963.
9. Kumar A, Zarychanski R, Pinto R, Cook DJ, Masrhall J et al. Critically Ill patients with 2009 influenza A(H1N1) infection in Canada. JAMA 2009; 302(17): 1872–1879.
10. Chlan L, Guttormson J, Tracy MF, Bremer KL. Strategies for overcoming site and recruitment challenges in research studies based in intensive care units. Am J Crit Care 2009; 18(5): 410–417.
11. Brooks CJ, Stephens JW, Price DE, Ford DV, Lyons RA, Prior SL, et al. Use of a patient linked data warehouse to facilitate diabetes trial recruitment from primary care. Prim Care Diabetes 2009; 3(4): 245–248.
12. Embi PJ, Jain A, Clark J, Bizjack S, Hornung R, Harris CM. Effect of a clinical trial alert system on physician participation in trial recruitment. Arch Intern Med 2005; 165(19): 2272–2277.
13. Quan S, Wu R, Morra D, Wong BM, Mraz R, Hamill M, et al. Demonstrating the BlackBerry as a clinical communication tool: a pilot study conducted through the Centre for Innovation in Complex Care. Healthc Q 2008; 11(4): 94–98.
14. Wu RC, Morra D, Quan S, Lai S, Zanjani S, Abrams H, et al. The use of smartphones for clinical communication on internal medicine wards. J Hosp Med 2010; 5(9): 553–559. doi:10.1002/jhm.775.
15. Simpson F, Sweetman EA, Doig GS. A systematic review of techniques and interventions for improving adherence to inclusion and exclusion criteria during enrolment into randomised controlled trials. Trials 2010; 11: 17.
16. Dugas M, Lange M, Berdel WE, Müller-Tidow C. Workflow to improve patient recruitment for clinical trials within hospital information systems – a case-study. Trials 2008; 9: 2.
17. Embi PJ, Jain A, Harris CM. Physicians' perceptions of an electronic health record-based clinical trial alert approach to subject recruitment: a survey. BMC Med Inform Decis Mak 2008; 8: 13.
18. Randolph AG. The unique challenges of enrolling patients into multiple clinical trials. Crit Care Med 2009; 37(1 Suppl): S107-S111.
19. McGregor J, Brooks C, Chalasani P, Chukwuma J, Hutchings H, Lyons RA, et al. The Health Informatics Trial Enhancement Project (HITE): Using routinely collected primary care data to identify potential participants for a depression trial. Trials 2010; 11: 39.
20. Foster D, Cook D, Granton J, Steinberg M, Marshall J. Use of a screen log to audit patient recruitment into multiple randomized trials in the intensive care unit. Canadian Critical Care Trials Group. Crit Care Med 2000; 28(3): 867–871.
21. Cook DJ, Blythe D, Rischbieth A, Hebert PC, Zytaruk N, Menon K, et al. Enrollment of intensive care unit patients into clinical studies: a trinational survey of researchers' experiences, beliefs, and practices. Crit Care Med 2008; 36(7): 2100–2105.