Clin. Cardiol. Vol. 24 (Suppl. V), V-14–V-16 (2001)

Electronic Prescribing via the Internet for a Coronary Artery Disease and Hypertension Megatrial

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Summary: A unique feature of the International Verapamil SR/Trandolapril Study (INVEST) is the Internet-based, electronic data capture system developed at the University of Florida for this trial. This system allows for direct collection of patient enrollment data, randomization, study drug prescribing, and real-time monitoring of patient data online. In this trial, immediate transmission of patient-specific data occurs using online data collection forms. Investigators only need a personal computer with access to the Internet; no complicated hardware, software systems, or paper storage files are necessary. INVEST is the first large randomized clinical trial to use electronic prescribing systems in the research setting. Electronic prescribing eliminates errors associated with illegible handwriting, inappropriate dosing, and inappropriate medication choice. Because the INVEST protocol allows flexibility of medication choice and dosage range within randomly assigned treatment strategies based on patient tolerance and blood pressure response, physician investigators may use individual practice patterns and preferences. The electronic system provides guidance to physicians relative to the addition of medication or dosage adjustments within the protocol. Electronic tracking and reporting mechanisms have enabled investigators in this complex megatrial to enroll, randomize, and manage patients in real time with great accuracy.

Key words: central drug distribution, clinical trials management, electronic prescribing, enrollment, INVEST, pharmacy, randomization

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Introduction

The rationale and design of the International Verapamil SR/Trandolapril Study (INVEST) has been described,[1] and further information regarding this study can be accessed via the Internet (http://invest.biostat.ufl.edu). Briefly, INVEST is a phase IV, prospective, randomized, open, and blinded endpoint (PROBE) clinical trial comparing a calcium antagonist strategy (verapamil SR) with a beta-blocker strategy (atenolol) for the control of hypertension in 22,599 patients with established coronary artery disease (CAD). A total of 862 physician investigators from around the world enrolled patients, beginning in September 1997 and ending in December 2000. Patient follow-up is scheduled to conclude in December 2002.

Electronic Data Capture—Interaction System

A unique feature of INVEST is the Internet-based, electronic data capture system that allows for completion of patient enrollment, randomization, study drug prescribing, and real-time monitoring of patient data online. All site investigators have direct and continuous access to the system via the World Wide Web. Immediate transmission of patient-specific data is possible with online data collection forms, which allow the administrative coordinating center, the pharmacy coordinating center, the sponsor, and other units (IRB, DSMC, etc.) to receive secure data without delay. Passwords and an encryption system, similar to that used by banks during wire money transfers and automated teller machine transactions, ensures the security of all information during the data-transfer process.

The management of hypertension is complex, especially among patients with coexisting CAD, and often requires multiple medications and aggressive dose escalation to achieve the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI) blood pressure control targets. Because the protocol allows flexibility of medication choice and dosage range within the protocol-defined strategy based on patient tolerance and blood pressure response, INVEST physician investigators may use individual practice patterns and preferences. The electronic system can provide guidance to physicians if they need to increase dosage

of a medication or add new medications to compensate for a patient's uncontrolled blood pressure, and helps to assure protocol compliance.

Because INVEST uses an electronic data capture system and commercially available antihypertensive medications, it is uniquely suited for the special electronic prescribing and centralized drug distribution system developed at the University of Florida for this trial. Centralization was difficult because of the international composition of the trial. A centralized system would have required each participating country to comply with the regulations of every other country. As a result, prescribing and dispensing procedures were customized specifically for each participating country. This article describes the prescribing and dispensing procedure developed for the United States (including Puerto Rico), where 17,154 (76%) of all INVEST patients were enrolled.

Electronic Prescribing

Electronic prescribing of medications[2,3] has been approved by about one half of the states in the United States. As a result, pharmacies in those states can legally fill prescriptions that are received electronically from a licensed physician. Using various insurance formularies, electronic prescribing can eliminate errors associated with illegible handwriting, inappropriate dosing, and inappropriate medication choice. Based on these advantages, the Institute for Safe Medication Practices has called for the elimination of handwritten prescriptions by 2003.[4] Despite the obvious advantages, most physicians in the United States do not use electronic prescribing. Use is limited in part because electronic systems are not currently available in many patient care areas and because specialized software systems are required to communicate with particular pharmacies. Furthermore, most U.S. physicians are not familiar with electronic prescribing and, because of this lack of familiarity, would not voluntarily choose an electronic system over the traditional paper mode. Electronic prescribing should increase as hand-held devices become more common, as software systems are developed to interface with them, and as the systems become more user friendly.

Even though electronic prescribing systems have been available for many years, INVEST is the first large, randomized clinical trial to use one in the research setting (Fig. 1). With this system, all site investigators have access to real-time data 24 h a day. Investigators do not need complicated hardware and software packages; the only requirement is access to the Internet via a common web browser and Internet provider. Medications and dosages allowed by the study protocol are programmed into the system so that all prescriptions are necessarily based on the strategy the particular patient is randomized to receive. All prescriptions are automatically adjudicated by the pharmacy upon transmission. Prescriptions printed and archived by the pharmacy are processed immediately, and are legible, appropriate, and delivered direct to the patient's home. At the time of this writing, INVEST site investigators in the United States have issued more than 80,000 electronic prescriptions, all transmitted direct to a central mail-order pharmacy contracted to process the prescriptions for the study. These prescriptions are randomly reviewed in real time by the INVEST pharmacy coordinating center staff for appropriate dose escalation based on blood pressure response and other quality assurance measures.

Centralized Drug Distribution

INVEST offers a total of 41 different dosage regimens to site investigators to control blood pressure in patients enrolled in INVEST. Because of the large number of treatment options, centralized research drug distribution was developed. Without centralized distribution, investigators would have been required to use a large amount of office space to store the treatment options, and many medications would have expired before reaching patients.

A mail-order pharmacy with electronic prescription service capabilities, Express Pharmacy Services (EPS), of Largo, Florida, was selected to process all INVEST prescriptions in the United States. The study sponsor (Abbott Laboratories/Knoll AG) provided EPS with branded study medication (Isoptin SR®, Mavik®, and Tarka®) that was used to fill electronic study prescriptions. Generic brands were utilized for

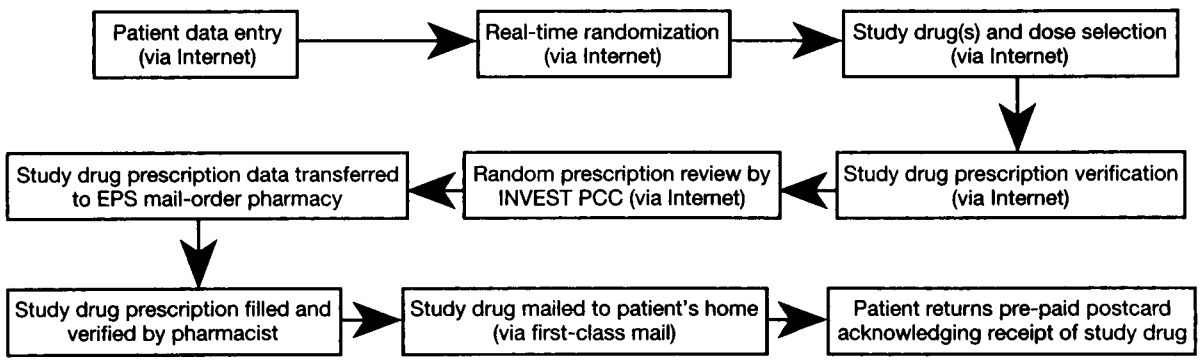

FIG. 1 Electronic prescribing via the Internet in the INternational VErapamil SR/trandolapril STudy (INVEST). *Abbreviations*: EPS = Express Pharmacy Services, PCC = pharmacy coordinating center.

atenolol and hydrochlorothiazide. At the time of this writing, EPS had dispensed approximately 13.6 million tablets of study drug pursuant to the 80,000 electronic prescriptions received for patients in the United States enrolled in INVEST. Rapid and ongoing accountability of study medications is possible because EPS provides daily electronic reporting of all prescriptions that have been filled. Additional tracking of medication occurs at the patient level. Express Pharmacy Services includes a self-addressed, prepaid postcard with each package of study medication sent to a patient's home, so that patients can acknowledge receipt of medications as they are delivered.

Conclusion

The development and use of central study drug distribution and electronic prescribing systems has allowed INVEST to enroll and manage a large number of patients rapidly throughout the world. In the United States and Puerto Rico, the Internet-based, electronic data capture system allows for completion of patient enrollment, randomization, study drug prescribing, and real-time monitoring of patient data online. In addition, electronic tracking and reporting mechanisms have enabled the drug accountability process to occur with great accuracy in real time at many levels. Research physicians and pharmacists can check the accuracy of what was prescribed and dispensed by use of the electronic system, which can then be confirmed by the patient's postcard acknowledgment. This technology has enabled the investigators in this complex megatrial to enroll, randomize, and manage patients in real time with great accuracy.

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