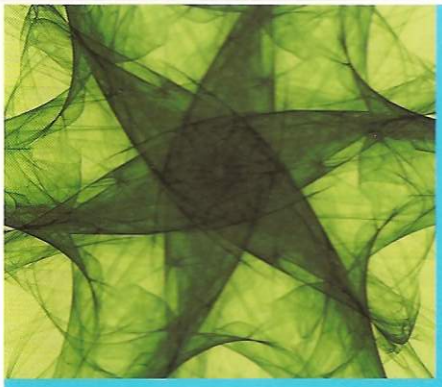


SPECIAL FEATURE:

Beyond Electronic Data Capture (EDC):

The Use of Decision Support Systems to improve Patient Safety and the Quality of Patient Care in Clinical Trials

By Stephen Goundrey-Smith MSc Cert Clin Pharm MRPharmS Steve Higham PhD, Andy Collinson BSc , Mark Dale MB ChB MRCPsych

ELECTRONIC SYSTEMS ARE INCREASINGLY BEING USED TO MANAGE MULTICENTRE CLINICAL TRIALS. THESE SYSTEMS DEAL WITH THE ELECTRONIC CAPTURE OF DATA ON PATIENTS ENROLLED IN THE TRIALS – FROM PATIENT PROFILES, TO LABORATORY TESTS AND DIAGNOSTICS. AS WELL AS SYSTEMS DEVELOPED BY THE PHARMACEUTICAL COMPANIES SPONSORING CLINICAL TRIALS, THERE ARE A NUMBER OF BESPOKE SOFTWARE SYSTEMS ON THE MARKET TO ENABLE ELECTRONIC DATA CAPTURE (EDC) FOR CLINICAL TRIALS MANAGEMENT. THESE INCLUDE, FOR EXAMPLE, APPLICATIONS SUCH AS DMSYS (SIGMASOFT) AND CLINICAL ASSET MANAGEMENT (KIKA MEDICAL SYSTEMS)

THESE SYSTEMS ARE generally web-based and enable consistent capture and transmission of patient data in a multicentre trial. They thus ensure that the trial is supported by high quality data that has been collected in a cost-effective manner, which in turn improves patient safety and reduces the risk of medical errors in the care of patients in clinical trials.

However, while EDC is an important aspect of the use of modern technology in the management of clinical trials, there are some aspects of medical practice in clinical trials that require more than simply the capture of data – where sophisticated medical decision support is required at the point of prescribing. This is an emerging area of technology application in clinical trials.

CONCOMITANT MEDICATION MANAGEMENT

One such aspect where decision support has an application is the monitoring of concomitant prescribing in clinical trial patients. A clinical trial protocol may have detailed requirements for restriction of co-prescribed drugs and yet, at present, there is no standard system to alert healthcare professionals to these restrictions.

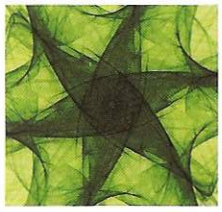
This is a significant problem because protocol violations due to inappropriate concomitant medication can lead to:

1. Variations in treatment between centres in multi-centre trials
2. Risks to patient safety and quality of care, and
3. Costs to the pharmaceutical industry and other sponsors due to attrition of patient numbers in clinical trials.

The standard practice of the pharmaceutical industry is to provide hard copy documentation on concomitant prescribing restrictions for clinical trial patients to investigators and monitors. Investigators, monitors and their teams then need to check a patient's medication against the exclusion criteria for the trial using standard formularies of drug information resources. 95% of trial monitors use traditional paper-based formularies and, for this reason, are often restricted to trial monitoring in specific clinical specialities.

Because the current practice relies purely on human intervention at different stages of patient care to assess possible drug interactions, protocol violations often occur because concomitant prescribing has already taken place inadvertently, once the patient has been enrolled in the clinical trial. Sometimes, investigators and healthcare professionals do not correctly match medicines prescribed to the patient with trial exclusion groups. Sometimes it is not clear what drugs are excluded or not, especially if the exclusion criteria are based on groups of medicines based on pharmacological properties or metabolic characteristics. In addition, some therapeutic areas (e.g. neurology) have lengthy and complex trial exclusion criteria for medicines.

It is estimated that protocol violation occurs in as many as 5% of clinical trial patients per year as a result of inappropriate concomitant prescribing.

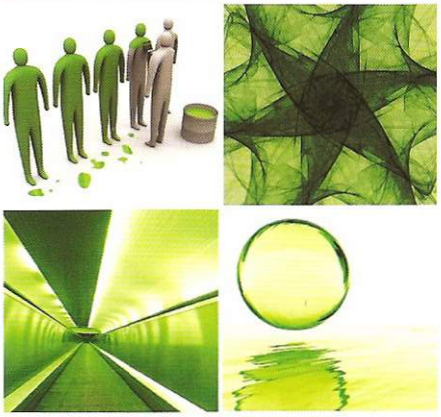


Stephen Goundrey-Smith

SPECIAL FEATURE:

Beyond Electronic Data Capture:

The Use of Decision Support Systems to improve Patient Safety and the Quality of Patient Care in Clinical Trials?



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Attrition of patient numbers in a clinical trial is very costly to the pharmaceutical industry. The typical cost associated with each patient in a Phase III clinical trial is $26,000. Data from the US clinical trials registry database ClinicalTrials.gov from 2006 to 2008 indicated the total cost for enrolled patients with medication violations to approximate to $750 million dollars annually for the top 10 pharmaceutical companies.

Furthermore, depending on the design, patient numbers and power of a study, the loss of just one patient from the per protocol analysis in some studies is enough to render the study invalid. This situation has been observed in trials of a cannabis-based preparation in patients with multiple sclerosis[11].

CONCOMITANT MEDICATION MANAGEMENT – THE CHALLENGE TO PHYSICIANS

Concomitant medication management for patients in clinical trials presents a challenge to all doctors, not just those employed by the pharmaceutical industry with responsibility for oversight of clinical research.

The consequences of including a patient inappropriately into a study are well known and potentially catastrophic. They place the patient at risk from serious pharmacokinetic drug interactions. Furthermore, they place the investigator at risk as indemnity provided may not include cover for protocol violations.

General Practitioners are provided with information in paper format to assist with management of medications they may wish to prescribe to their patients that are enrolled in a clinical trial under the care of another investigator. It is recognised that many family doctors do not read this information often because it is not circulated amongst partners within the practice. To complicate matters further they may well have numerous patients enrolled in a variety of studies. There are well documented errors through inappropriate prescribing which occur by lack of awareness of the protocol or that the patient is in a clinical trial.

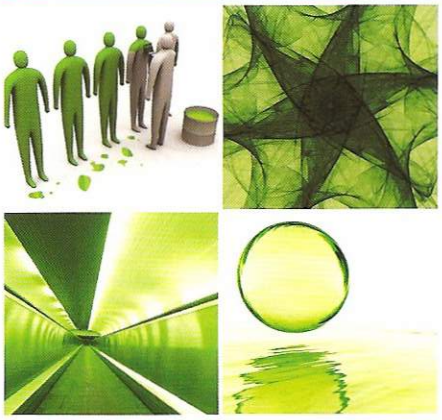
Hospital-based clinicians face an additional problem in that they are unlikely ever to have seen information relating to the protocol and may well be providing urgent treatment. Inability to access this information in a timely manner is of particular importance when medications are excluded for major safety reasons.

ELECTRONIC DECISION SUPPORT TECHNOLOGY IN MEDICINE

During the last twenty years, drug databases have been developed to allow clinical decision support in prescribing and medicines management. Decision support in prescribing is now used routinely within GP practice systems, hospital electronic prescribing systems and pharmacy systems. Furthermore, it is recognised that this decision support can enhance clinician performance in drug dosing and preventive care decisions[12].

Some work has been done with electronic decision support at the point of clinical trial enrolment in breast cancer trials. The OncoDoc system[13] is a browsing tool using a decision tree knowledge base, which matches patient details to available clinical trials protocols, and directs prescribers towards appropriate clinical trials or other therapeutic options. This application was found to be successful in improving compliance with protocols and guidelines and also increasing patient enrolment in clinical trials. This latter finding is particularly relevant given the fact that protocol violation is a major cause of clinical trial attrition rates in major clinical trials.

The techonology therefore exists to alert the prescriber at the point of prescribing concerning drug interactions and well-designed decision support in e-



prescribing systems has the potential to improve the prescriber's awareness of drug interactions, and improve treatment quality[4].

Drug datasets for drug interaction alerting are increasingly sophisticated and, as well as identifying individual drugs, these databases now have the rules to identify drugs of a particular chemical group (e.g. phenothiazine anti psychotics), therapeutic use (e.g. antiparkinson agents) or pharmacological characteristics (e.g. CYP2C19 inhibitors).

A typical set of concomitant medication exclusion criteria for a clinical trial protocol might be:

- Exclude CYP2C19 inhibitors
- Exclude all drugs to treat Parkinson's disease
- Restrict conventional neuroleptic and antidepressant drugs
- Exclude drugs with potential to cause Torsades de Pointes
- Patient must be taking a cholinesterase inhibitor
- Exclude warfarin, heparin and ticlopidine
- Dose restriction of paracetamol

It is therefore possible to support complex requirements in concomitant prescribing monitoring in clinical trial patients using the available drug decision support technology for drug interactions. This may also have a beneficial effect on patient recruitment into trials as well as patient safety.

TOWARDS A CONCOMITANT MEDICATION MONITORING SERVICE

The use of drug decision support technology to monitor concomitant prescribing and protocol exclusions in clinical trial patients is a useful development, with the potential to reduce time spent by clinicians and other health professionals in clinical trial monitoring.

Furthermore, the use of centralised drug decision support to deal with concomitant medication monitoring represents a step ahead from the EDC technologies that have been developed to date.

The ideal system for centralised concomitant medication monitoring in clinical trials would have the following features:

- Rapid checking of prescribed medicines against protocol rules at the point of prescribing in real time
- Web-based for ease of use and scalability.
- ASP.net architecture or equivalent to enable straightforward integration with other systems used by both sponsors and investigators, such as clinical data management systems in the pharmaceutical industry and electronic prescribing and pharmacy systems used by health providers.
- GCP and other clinical regulatory compliance.
- Reporting on concomitant prescribing, per trial, per investigator and per subject.
- Drug database and rules should be highly configurable and the service should include pharmacy and therapeutics expertise.
- Designed for global use, and configurable for different languages and cultures.

The ideal solution will allow concomitant prescribing in clinical trials to be managed in a centralized way, in the same way that diagnostics and laboratory tests can be, but with the added value of sophisticated decision support for drug-related protocol exclusions. The CliniSafe system is currently the only system that has addressed these requirements (www.clinisafe.com)

CONCLUSIONS

Efficient oversight of clinical trials is essential to ensure the integrity of clinical research. EDC systems for clinical trials have been developed to ensure efficient and cost-effective collection and standardization of trial data. Their contribution to clinical research has been accepted and valued by sponsors and investigators alike. However, decision support functions add value to EDC and can have a major impact on appropriate patient management and most importantly the safety and quality of care of patients enrolled in clinical trials.

Decision support systems have been shown to be of benefit to support medical consultations in general, and in other areas of clinical trials management. Drug decision support systems, which have been in use in general medical practice for some years, are now able to support central concomitant medication monitoring in

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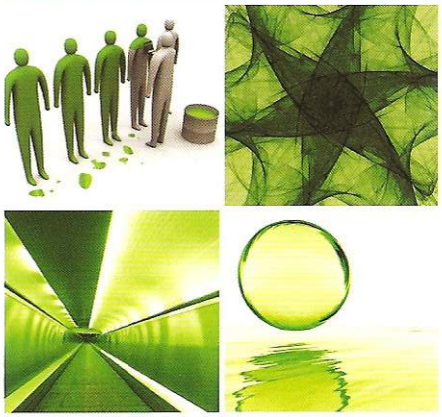

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patients on complex clinical trial protocols.

These systems, which enable complex drug decision support in real time, enable maximum success from clinical trial programmes for sponsors and investigators and enable physicians – both employed by the pharmaceutical industry, and in clinical practice - to deliver the best quality care to patients enrolled in clinical trials.

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