

A Web-based Electronic Concomitant Medication Management System

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Over the past 15 years, there has been documented major change in the world map when it comes to the conduct of clinical trials driven by the emergence of new economic super powers, such as China, and the increasing competition faced by biopharmaceutical companies and Contract Research Organizations (CROs) for patients to enroll.

ClinicalTrials.gov currently includes trials registered in 179 countries. To put this in perspective, the United Nations has 193 members. It is fair to say that clinical trials have reached the four corners of our diverse world.

Around one-third of Phase III trials have actively recruiting sites in China, Russia and the Latin America region. India, Mexico and the Middle East also make up a significant proportion. Add to this mix the US, Europe and Japan, and you'll find a series of logistical challenges. The focus of this article is on how to safely manage the important safety issue of concomitant medication. It describes at the positive impact of using a web-based electronic concomitant medication management system in study protocol design both from a perspective of global standardization and efficiency improvements in the data management workflow.

The Challenges

During the life cycle of large trials, sites can be closed due to lack of patient recruitment and sites from new countries added. Considering that trial protocols are often prepared well in advance of selecting the country where a trial will be conducted, this can occur months or even years after the protocol was initially designed. Additional countries, new medications and changing protocols demand a concomitant medication management system which is both constantly updated and interactive.

When you are enrolling patients in a trial, in whichever country that may be, one has to make sure, that they are eligible for the study and not excluded due to a concomitant medication. Global variation in names of branded and generic drugs creates a challenge for the clinical research professionals designing the protocol, for the database programmers and for the investigators who have to make decisions on the ground.

Drug-drug interactions in clinical practice are a common problem during drug treatment. These interactions give rise to a large number

of hospital admissions as a result of medically important, sometimes serious or even fatal adverse events. Drug-Investigational Product interactions during a clinical trial also pose this risk and can, in addition, cause partial or complete abolishment of treatment efficacy. The aging population, where polypharmacy is more common, increases the likelihood of such interactions.

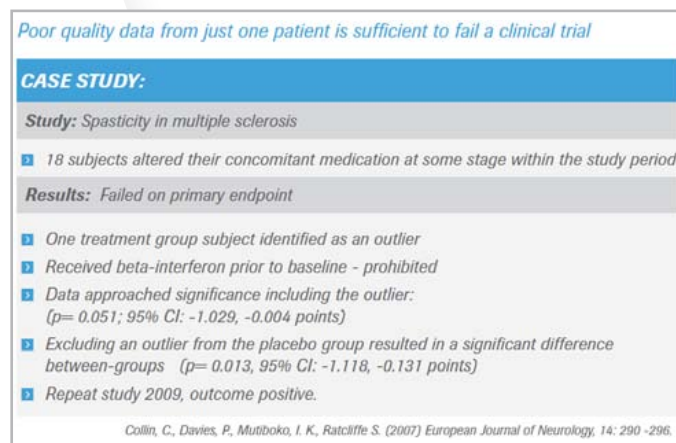


Figure 1 – Case study from Collin, C. Davies, P. Mutiboko, I.K., Ratcliffe S. (2007) European Journal of Neurology, 14: 290-296.

A clinical trial protocol may have detailed requirements for restriction of co-prescribed drugs yet, at present, only a small number of trials benefit from using electronic concomitant medication management systems.

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,
3. Data management queries which need to be resolved, and
4. Delays in the delivery of R&D pipelines of the pharmaceutical industry due to attrition of patient numbers in clinical trials.¹

The Traditional Approach

The standard practice of the pharmaceutical industry is to provide hard copy documentation to investigators and monitors detailing concomitant prescribing restrictions for clinical trial patients. 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. Ninety-five per cent of trial monitors use traditional paper-based formularies and, for this reason, are restricted to trial monitoring in specific clinical specialities.²

Because the current practice relies purely on human intervention at different stages of patient care to assess possible drug interactions,

Continued on page 14

A Web-based Electronic Concomitant Medication Management System

Continued from page 13

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 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.

"In the current process, the study sponsor reviews the scientific literature, drug interaction databases, and previous study results to identify such drugs. It then lists them in the eligibility criteria.

Potential problems with the list include the following:

1. Study personnel may be familiar with a generic or a trade name, but not the other(s).
2. A prohibited drug may be an ingredient in a combination drug.
3. If a class of drugs, e.g., opiates or nonsteroidal anti-inflammatories, is listed instead of the individual drugs, study personnel may not be aware that a specific drug is in the prohibited class. This problem is more severe if a group of medications is prohibited based on its pharmacological properties or metabolic characteristics.
4. The restrictions may be complicated, e.g., against the combined use of more than one hypertensive drug from a class.
5. There may be unacceptable dosages of otherwise acceptable drugs.
6. Any ambiguity requires interpretation by the study coordinator or investigator.
7. Some therapeutic areas (e.g., neurology) have exceptionally lengthy and complex exclusion criteria.
8. Drug names may vary by country.
9. There may be too many drugs on the list for the study coordinator and site monitor to remember or scan reliably.
10. A list organized alphabetically or by class may be unintuitive for some people.
11. Drugs may need to be added to or removed from the list during the course of the study.
12. The list may be prefaced with the caveat, "This does not represent a complete list."

When groups of drugs are excluded by category from the protocol, the exclusion is often illustrated by a few examples from within the category. This list is rarely comprehensive. An example set of rules that may be required for a protocol is shown below:

1. Exclude CYP2C19 inhibitors, e.g., Fluvoxamine, Isoniazid, Ketoconazole.
2. Exclude drugs to treat Parkinson's disease.

3. Restrictions on the use of conventional neuroleptic and antidepressant drugs.
4. Exclude drugs with the potential to cause Torsades de Pointes.
5. Patient must be taking a stable dose of a cholinesterase inhibitor, e.g., Donepezil.
6. Exclude warfarin, heparin and ticlopidine.
7. Dose restriction of paracetamol.

It is unreasonable to expect study personnel to reliably handle long, complicated or ambiguous lists of prohibited drugs. Given the risks to subject safety and scientific validity, minimizing the chance of human error with computerized decision support makes sense."³

In these global trials information on concomitant medications used in addition to the study medication are collected and recorded on relevant Data Collection Instruments. Any medical coding dictionary and all subsequent revisions have to be correctly imported in the appropriate coding tool by the database programming team.

Electronic Concomitant Medication Management

Drug databases have been developed to allow clinical decision support in prescribing and medicines management. Decision support in prescribing is now used routinely within General Practitioner practice systems, hospital electronic prescribing systems and pharmacy systems.

The use of drug decision support technology to monitor concomitant prescribing and protocol exclusions in clinical trial patients is an important development, with the potential to reduce time spent by physicians and clinical trial monitors.

The ideal system for centralized concomitant medication management in clinical trials would have the following features:

1. Rapid checking of prescribed medicines against protocol rules at the point of prescribing in real time.
2. Web-based for ease of use and scalability.
3. Designed for global use, and configurable for different languages, cultures and drug databases.
4. Good Clinical Practice and other clinical regulatory compliance.
5. Validated Software and Validated Drugs.
6. Drug database and rules should be highly configurable.

Use of a web-based service, such as CliniSafe®, allows protocol drug rules to be set up electronically. This enables checking of medications before a patient is enrolled in a trial, thereby eliminating errors, supporting recruitment, and, crucially, improving patient safety.

Harmonization of medication management reduces deviation from a trial protocol and data variability. Constantly providing live feedback to the sites and monitors ensures that awareness is maintained throughout the trial. This will have a significant impact on ease of concomitant medication tabulation, the numbers of concomitant

Continued on page 15

A Web-based Electronic Concomitant Medication Management System

Continued from page 14

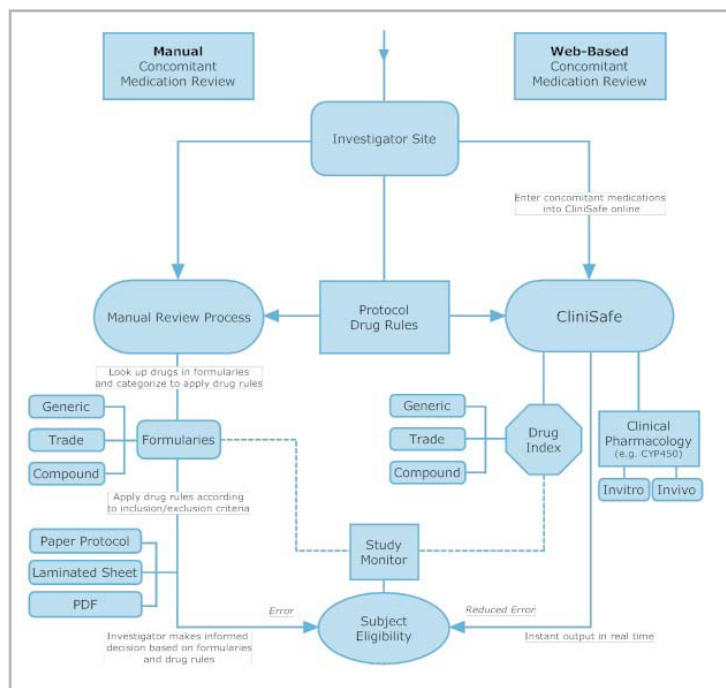


Figure 2 – Flow Chart for Comparison of Manual and Web-based Concomitant Medication Management

medication queries generated and assist with resolution of those which arise.

The system checks concomitant medications against rules programmed specifically for a study and is configurable for use on multiple drug databases including, but not limited to the WHO Drug Dictionary and CliniSafe's own Drug Index.

Summary

Use of an automated and scalable solution for the management of concomitant medication in global trials is a logical step forward in clinical research much in the same way as the advance from paper CRFs to electronic data capture. This will not only benefit the patient and the investigator, but also the organization running the clinical trials. ■

References

- 1 – Collin, C. Davies, P. Mutiboko, I.K., Ratcliffe S. (2007) *European Journal of Neurology*, 14: 290-296.
- 2 – CRA Survey, "Monitoring Concomitant Prescribing Restrictions" (feedback based on 43 respondents) carried out by MAC Neuroscience, 2010
- 3 – Dale, Mark. Goundrey-Smith, Stephen. Higham, Steve. Collinson, Andy. (2010) *Journal of Clinical Research Best Practices*, 6:1-5.