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Reducing Human Error in Checking Concomitant Medications

By Mark Dale, Stephen Goundrey-Smith, Steve Higham and Andy Collinson

Subject safety and scientific validity require sites to avoid enrolling subjects who are taking certain "concomitant" medications ("conmeds") and to properly handle enrolled subjects who start taking these medications. In a typical study, the coordinator screens potential subjects against the list of prohibited (i.e., restricted) medications in the protocol's eligibility requirements. Later, if the person enrolls in the study, the coordinator checks for problems with any new medications. The investigator presumably reviews the coordinator's work. The site monitor verifies that the coordinator did not miss any prohibited medications. After data lock, the scientists and biostatisticians review the data to catch any remaining problems.

This system relies on three troubling assumptions:

- The list of prohibited medications is complete and unambiguous.
- The coordinator or site monitor correctly identifies prohibited medications from the list.
- Subject safety and the scientific validity do not require timely identification of prohibited medications.

Analysis of data from 15 studies found that concomitant medication problems constituted 5.1% of protocol violations (Table 1). Paper-based systems are, of course, prone to human

Table 1. Frequency of Concomitant Medication Problems

Therapeutic Area	Study Drug	Proportion of Protocol Violations that are Conmed	Reference
Gastrointestinal	Humanized monoclonal antibody	5.9%	1
Infection	Antithrombin III	9.3%	2
Pain	Paracetamol, aspirin and ibuprofen	1.6%	3
Oncology	Palonosetron	2.5%	4
Respiratory	Moxifloxacin	1.6%	5
Cardiovascular	Tezosentan	4.9%	6
Pain	Paracetamol or parecoxib	7.2%	7
Peptic Ulcer	Rabeprazole and omeprazone	16.3%	8
Gastrointestinal	Bisacodyl	3.6%	9
CNS	Hypericum extract WS® 5570	4.9%	10
Immune system	Mycophenolate Mofetil	1.9%	11
Gastrointestinal	Esomeprazole	2.0%	12
Pain	Tramadol	5.2%	13
Respiratory	Varimax	7.8%	14
Haematology	Xa inhibitor LY517717	2.2%	15
	Mean	**5.1%**	

error. Electronic case report form ("eCRF" or "EDC") systems could catch prohibited medications in an automated and semi-timely manner, but, remarkably, do not include this feature. This article describes an Internet-based system that study coordinators, site monitors, and eCRF systems could use to check conmeds quickly and reliably.

Prohibited Medications

Prohibited medications fall into three types:

- Drugs that interact with the study drug
- Drugs that diminish liver or kidney function, or otherwise raise pharmacokinetic or safety issues
- Drugs that produce confounding effects, such as masking or enhancing the intended benefits or potential side effects of the study drug

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:

- Study personnel may be familiar with a generic or a trade name, but not the other(s).
- A prohibited drug may be an ingredient in a combination drug.
- 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.
- The restrictions may be complicated, e.g., against the combined use of more than one hypertensive drug from a class.
- There may be unacceptable dosages of otherwise acceptable drugs.
- Any ambiguity requires interpretation by the study coordinator or investigator.
- Some therapeutic areas (e.g., neurology) have exceptionally lengthy and complex exclusion criteria.
- Drug names may vary by country.
- There may be too many drugs on the list for the study coordinator and site monitor to remember or scan reliably.
- A list organized alphabetically or by class may be unintuitive for some people.
- Drugs may need to be added to or removed from the list during the course of the study.
- The list may be prefaced with the caveat, "This does not represent a complete list."

When groups of drugs are excluded from the protocol by category, 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:

- Exclude CYP2C19 inhibitors, e.g., Fluvoxamine, Isoniazid, Ketoconazole.
- Exclude drugs to treat Parkinson's disease.
- Restrictions on the use of conventional neuroleptic and antidepressant drugs.
- Exclude drugs with the potential to cause Torsades de Pointes.
- Patient must be taking a stable dose of a cholinesterase inhibitor, e.g., Donepezil.
- Exclude warfarin, heparin and ticlopidine.

- 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.

Computer-Assisted Prescribing

Two types of computer-based systems are widely used to help physicians prescribe correct medications. Decision-support systems guide the physician through the prescribing process with a series of questions, such as potential medication conflicts. Drug interaction alerting systems just focus on notifying the physician or pharmacist of potential medication conflicts.

A meta-analysis of 68 controlled trials of clinical decision support systems found that clinical decision support can significantly enhance clinician performance in drug prescribing and study quality.[16]

The value of clinical decision support in primary care and ambulatory care settings has also been highlighted. A U.S. study of a commercial e-prescribing system with drug decision support functions used by 15 community health providers showed a sevenfold reduction in prescribing errors.[17]

Drug datasets for drug interaction alerting are increasingly sophisticated. In addition to identifying individual drugs, these databases have rules to identify drugs of a particular chemical group (e.g., phenothiazine anti psychotics), therapeutic use (e.g., anti-Parkinson's agents), or pharmacological characteristics (e.g., CYP2C19 inhibitors). These databases can support complex requirements for concomitant medications in clinical trial patients using the available drug decision support technology for drug interactions.

A Concomitant Medication Monitoring System

A new web-based system, CliniSafe™, enables study personnel to check conmeds in real time. The study coordinator, for example, logs into the system for the study and enters the subject's medications to be checked. CliniSafe then informs the coordinator if there is a problem and which study drug rule would be violated, e.g., "Amiodarone is a moderate CYP4502D6 inhibitor and cannot be taken within 28 days of visit 1."

CliniSafe provides centralized concomitant drug checking, ensuring that even complex drug rules are applied with a standardized approach. The system can be configured for use in multiple localities and languages. Reports can be generated for safety monitoring. Databases of patient drugs can be screened to enhance subject recruitment. CliniSafe can also be integrated into eCRF systems, although the results would not be as timely. Medications entered once can be saved to speed up future review or subsequent study visits. Multiple drugs can be checked in a single query.

CliniSafe checks conmeds against rules created exclusively for the study and is configurable for simultaneous use on multiple drug databases, such as the UK dmd, the WHO Drug Dictionary, the FDA approved list of drug products, or the CliniSafe Drug Index. These comprehensive databases are constantly updated.

It takes approximately one minute for a coordinator to check five medications offering considerable time savings in relation to reviewing paper protocol and paper formularies.

Summary

Safety monitoring is becoming more and more important in clinical research. As eligibility criteria become ever more complex, human error becomes more likely, with significant implications for subject safety and scientific validity. Automating the process of checking conmeds will reduce human error and save time.

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