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Assisted prescribing: Clinical decision support with MedSafety Scan now available ☆,☆☆

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ABSTRACT

Too often, adverse events due to prescription medications are a cause of death and disability. Many of these events could be prevented, but most efforts to do so have had limited success, mainly due to the challenges of having the information that is necessary for safe prescribing available at the time when prescriptions are being written. Hospital-based Clinical Decision Support (CDS) systems are being developed to manage this information, identify at- risk patients, and help mitigate their risk of medication-induced harm. AZCERT, a non-profit created in 1999 with federal funding has helped hospitals develop these systems and has released an internet-based CDS program to assist in the safe prescribing of medications. This CDS program, MedSafety Scan, can be customized for any clinical venue and is available as an open-source program for all healthcare providers at www.medsafetyscan.org.

Introduction – rationale for assisted prescribing

There is no doubt that prescription medications can improve patient well-being and save untold numbers of lives. However, like many medical interventions, there can be unwanted and sometimes deadly adverse effects of medicines. The US Center for Disease Control and Prevention (CDC) estimates that prescription medications are one of the leading causes of death in the United States [1]. Recent concern for deaths due to the misuse of opiate medications, while absolutely important, often overlooks the fact that non-opiate prescription drugs are responsible for one of every four medication-induced deaths each year. [2]. The most recent CDC data (2017) show that the number of deaths due to prescription drugs was 73,990 and had tripled between 1999 and 2017. This was true even for the subset of persons over age 65 for whom narcotic drug abuse is less likely to be a contributing factor [3]. It is clear that adverse drug events (ADEs) are costly, not only due to the lives lost and the serious injuries, but also costly in monetary terms because they are associated with greater length of hospital stay and higher overall cost of care [4].

Yet, this is not a new problem nor one that has been ignored. In the 1990's, reports of a growing number of deaths caused by prescription medicines were the focus of major scientific publications (5), books (6, 7), and white papers, including two series of publications from the National Academy of Medicine's Institute of Medicine, i.e. "To Err is Human" (8) and the "Quality Chasm Series" (9, 10). These called attention to a growing number of deaths attributed to adverse drug reactions, preventable drug-drug interactions, inappropriate prescribing practices, and medication errors. There were numerous calls for efforts to reduce medication-induced harm. National policies were promulgated by Medicare and Medicaid that encouraged the use of information technology, electronic medical records and computerized provider order entry (CPOE) for prescription drugs (11). Congress held hearings on the problem and eventually authorized federal funding for programs intended to reduce the growing number of patients being harmed by medications and their misuse (12, 13). These efforts have met with some success, but the available evidence suggests that the problem is continuing to grow (3, 14). The purpose of this review is to summarize the current state of our knowledge of clinical decision support for optimal prescribing and introduce a newly available tool, MedSafety Scan.

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Initial efforts to improve medication prescribing

Many of the early efforts to prevent drug-induced harm were based on seemingly sound logic but often little, if any, strong evidence. For example, CPOE programs have been created to issue alerts when a patient is prescribed a drug that, according to the medical record, is thought to have previously caused an allergic reaction (15). Similarly, most CPOE programs notify prescribers when two or more drugs have the *potential* for serious drug-drug interactions (DDI). Yet, the impact of these CPOE alerts for allergies or DDI has been dramatically constrained because 70–95% are routinely over-ridden by prescribers, often for valid reasons (16). In this and many other healthcare settings, "alert fatigue" has become a serious problem. In response, expert consensus panels have published guidelines and principles for how to design effective medication alert strategies (17) but evidence of their effectiveness has mostly been limited to changes in the process of care delivery (18), not in clinical outcomes.

In 1997, Congress authorized federal funding for a network of Centers for Education and Research on Therapeutics (CERT) with the mission to improve therapeutic outcomes. One of these fourteen centers, the Arizona CERT (AZCERT), developed and evaluated efforts designed to prevent adverse drug reactions and drug-drug interactions, especially, but not limited to, those that result in QT prolongation and increased risk of torsades de pointes (TdP) (19–23). In general, AZCERT research has identified two basic impediments to any effort intended to prevent or minimize medication-induced harm:

1) Prescribers face overwhelming "information overload." They are expected to know massive amounts of detailed information about the medications that they and their colleagues prescribe and also know their patients' many medical (and social) conditions and diagnoses that are relevant and which could influence drug response.
2) Clinically important facts and data are often not available when prescribing decisions are being made due to our fragmented healthcare delivery systems and their siloed databases.

Innovations in decision support for assisted prescribing

Based on these conclusions derived from over two decades of research and, due to seeing only limited impact of efforts to educate the public and healthcare providers on the safe use of medicines, the AZCERT reached the conclusion that success would necessitate development and implementation of information management systems in the form of "Clinical Decision Support" (CDS) programs (19). If such CDS programs are to be adequately "informed" and therefore able to assist prescribers, they must have immediate access to two general types of data, 1) comprehensive information about the drug (s) that are being prescribed plus all other medicines already being taken and 2) information about the patient's medical condition to identify proven clinical factors that are likely to influence the patient's response to their medicines. Also, the CDS system must be programmed to operate in the background, integrate these two sources of data and present prescribers with actionable alternatives without unnecessarily interrupting their care of patients.

AZCERT, with funding from the FDA's Safe Use Initiative, developed a hospital-based CDS program that focused on the safe prescribing of QT-prolonging drugs. For its drug safety information, the CDS program utilizes AZCERT's QTdrugs list (24) and, for risk factor analysis, it uses a QT risk score developed and validated by Tisdale et al. (25). This CDS program is now operational in Banner Health, a system of 29 hospitals and medical facilities. However, even though Banner Health and many other hospitals and healthcare systems, including Mayo Clinic (26), Indiana University (25), Honor Health (Personal communication, Blackford A. Honor Health, Scottsdale, AZ; 2020) and hospital systems in Belgium (27) and the Netherlands, (28) have developed CDS programs to detect patients at risk of TdP, most healthcare professionals do not have such decision support available to assist their prescribing.

Table 1
MedSafety Scan features.

2• Patient-specific prescribing assistance
2• Accessible via internet
2• Facilitated medication list entry – RxNorm Standard drug name terminology with autocomplete and spellcheck
2• QT risk factor analysis tailored to clinical environment (ICU or non-ICU)
2• Drug-Drug Interaction (DDI) detection, tiered by severity
2• DDIs based on recommendations from CMS and in drug label
2• Identifies contraindicated drug combinations
2• Identifies therapeutic duplications based on ATC codes
2• Presents options for decision making, e.g. Check electrolytes, obtain ECG
2• Creates a report (PDF file) that can be filed or emailed to colleagues

For this reason, AZCERT has developed a web-based CDS program to assist prescribers that incorporates the general principles of its hospital-based system and has the flexibility to operate in various clinical environments. This open-source CDS program, MedSafety Scan®, can be accessed by healthcare providers at https://www.medsafetyscan.org/. With MedSafety Scan (MSS), all healthcare providers now have ready access to the QTdrugs list of QT-prolonging drugs, rapid QT risk assessment for their patients and the decision support they need for more informed and safe prescribing. In addition to QT risk assessment, MSS has other useful features such as those listed in Table 1 and discussed below.

How to access MedSafety Scan for decision support and assisted prescribing

Any healthcare provider with internet access can use MSS to obtain prescribing assistance that is automatically personalized for each of their patients. Fig. 1 shows the homepage for MSS where potential users can register and login to create a free account that allows them to enter and analyze patient data. The homepage includes links to brief videos that serve as an introductory guide for first-time users. One video introduces how to use MSS and the other is an example of MSS' analysis of a real clinical case of drug-induced TdP.

New users are first asked to create a "site" for their patients' records and to designate whether the site is for "ICU" or "Non-ICU" patients. This designation configures the site and selects the algorithm for QT risk factor scoring that will drive their patients' TdP risk assessment. The "ICU" configuration uses the QT risk score algorithm developed and validated for ICU patients by Tisdale et al. (25) The "Non-ICU" configuration uses a QT risk scoring model that has many of the same factors in the Tisdale score but includes additional risk factors that have been validated in inpatient populations from tertiary care hospitals (26–28). Table 2 lists the risk factors and their relative scores for the "ICU" (Tisdale) and "Non-ICU" (MSS default) risk models.

Once a site has been configured, individual patient records can be created by clicking "Add Patient". Fig. 2 is a screenshot of the data entry screen with light red shading to highlight the four general work areas: 1) Clinical Profile Entry, 2) Medicines List Entry, 3) Advisories, and 4) Care management plan. Fig. 3 shows the screen after a typical set of data has been entered. In this case, the data are for the clinical case of TdP that is presented in the video on the MSS website. By simply checking boxes, the relevant clinical

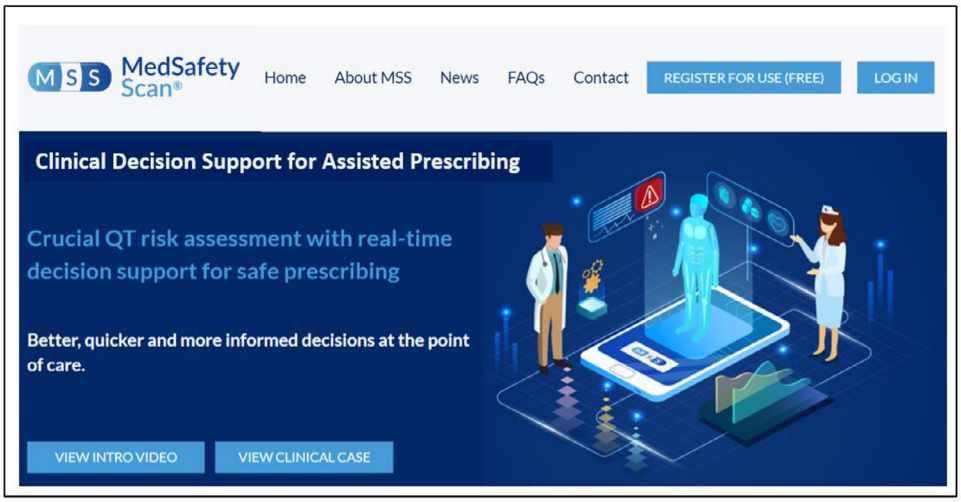

Fig. 1. Screenshot of MedSafety Scan website homepage.

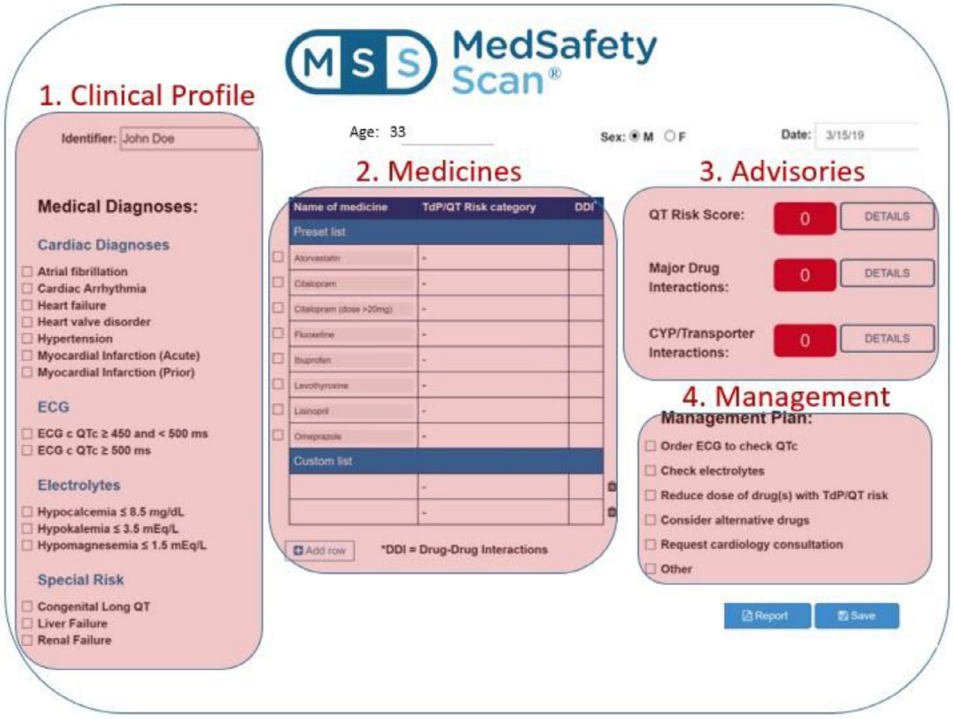

Fig. 2. Screenshot of data entry screen for MedSafety Scan with shading to designate the four work areas: 1) Clinical Profile Entry, 2) Medicines List Entry, 3) Advisories reported and 4) Management Plan record. (For interpretation of the references to color in this figure, the reader is referred to the web version of this article.)

data and elements of the patient's risk profile are easily entered. The patient's current medicines and any new ones being considered can be entered via the keyboard and the program recognizes any brand or generic drug listed in the NIH's RxNorm standard terminology database. Entry of a list of medications is facilitated by rapid-response, autocomplete and spellcheck functions. Entering the actual daily dose for drugs is optional since dosage is not currently considered in the risk analysis but could later be useful to have in the record. As data are entered, the system reports each drug's QTdrugs risk category (e.g., Known Risk of TdP, Possible Risk or Conditional Risk) and automatically calculates the patient's QT risk score. If one or more of the entered drugs are in the Known Risk of TdP category **and,** if the risk score exceeds any of the algorithm's preset thresholds, the user is notified of either Moderate, High or Very High risk of TdP. Fig. 3 also shows the following Torsades alert that is issued for the clinical case of TdP presented in the video: *"Very High Risk of TdP. Suggest replacement of ondansetron, hydroxychloroquine or ciprofloxacin with alternative drug (s) that are without Known Risk of TdP, if feasible."*

One of the strengths of MSS is that it allows the user to control and titrate the display of information that is available. MSS allows the user to choose when they wish to request access to the information and at any depth or level of complexity. For example, clicking on the QT risk score's "Details" box displays a popup (Fig. 4) that lists each of the risk factors that contributed to the patient's total QT risk score and a graph that gives context by showing where the patient's score falls in a distribution of similar patients (e.g. ICU or non-ICU). Also, instead of crowding the home screen with multiple drug-drug interaction (DDI) messages, MSS displays a check mark in the "DDI" column to identify those drugs

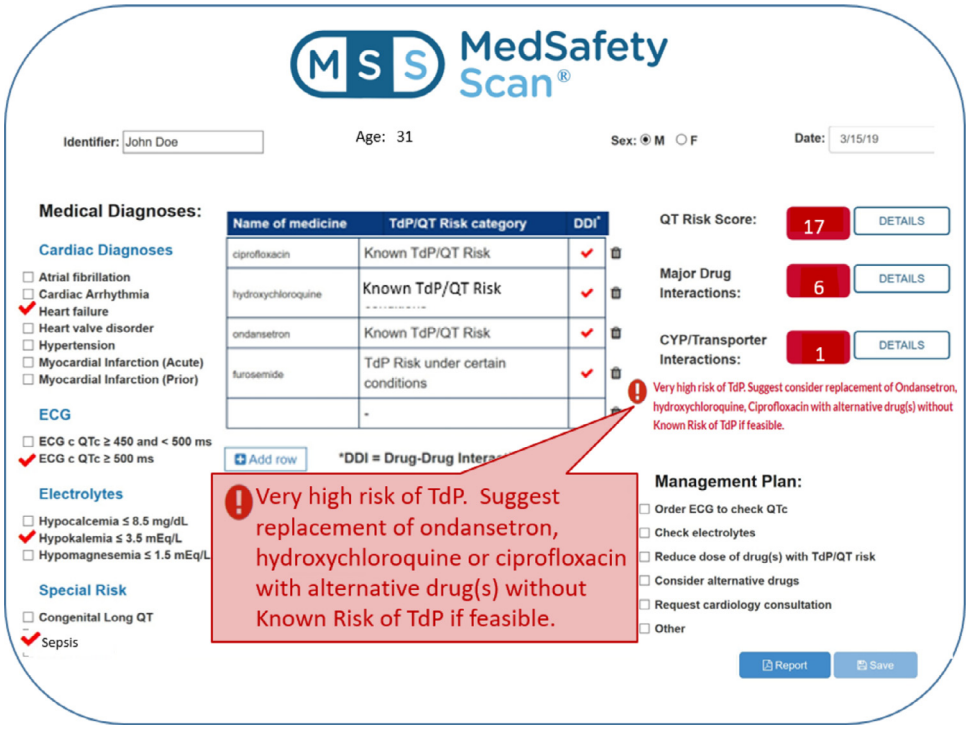

Fig. 3. Screenshot of MedSafety Scan data entry page with data entered for a clinical case. The TdP risk advisory is shown magnified in the shaded red call out box. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Comparison of QT risk factor scoring algorithms for ICU (Tisdale) or non-ICU configurations

	QTc Risk Score	
Risk Factor	Tisdale – "ICU"	MSS - "Non-ICU"
Age ≥ 65 y	1	1
Female Sex	1	1
Loop diuretic	1	-
Serum K^+ ≤ 3.5 mEq/L	2	3
Serum Mg^{++} ≤ 1.5 mEq/L	-	2
Serum Ca^{++} ≤ 8.5 mg/dL	-	1
Admission QTc ≥ 450 ms	2	3 or
QTc ≥ 500ms or CLQTS	-	8
Myocardial infarction	2 (acute MI)	3 (acute), 2 (prior)
Sepsis	3	-
Heart failure	3	3
Atrial Fibrillation	-	3
Heart Valve disorder	-	2
Hypertension	-	2
Known Risk TdP drugs (each)	3 (max. 2 drugs)	3
Possible Risk TdP drugs (each)	-	1
Known Risk TdP c Metabolic Inhibitor	-	2
Possible Risk TdP c Met. Inhibitor	-	1
Maximum Score	21	29 + drugs

that have potential interactions. When the user is ready to review the DDIs, they can click on the "Details" box to see the list of potential interactions ranked by severity. Also, those familiar with the FDA's CYP450 labeling convention for potential DDIs may want to click on the Details button for "CYP/Transporter Interactions."

Because of the documented and substantial inconsistencies between commercial DDI detection programs (29, 30), AZCERT has developed a novel DDI detection program for MSS. MSS is designed to only report DDIs that are included in the official drug label or those recommended by the Centers for Medicare and Medicaid Services (CMS) as serious (31). The DDIs are tiered by severity and their display can be filtered by thresholds that can be selected by the user as part of the site configuration. Table 3 lists the three general types of severity levels for DDIs that are reported in MSS.

MedSafety Scan provides case-specific advice

After MSS notifies the user of a risk of TdP and/or DDIs, it makes patient-specific suggestions for management of that risk. For example, when the QT risk score is above a set threshold and if the list of medicines includes one or more drugs with Known Risk of TdP, MSS advises "Suggest replacement of [drug name] with alternative drug without Known Risk of TdP." For patients taking multiple QT prolonging drugs, advice is given to "Consider checking ECG to monitor QT." For high-risk patient's taking a loop diuretic, a suggestion is given to "Consider checking electrolytes." If one of the patient's risk factors includes electrolyte imbalance, such as hypokalemia, the following message is given "Consider correcting hypokalemia before administering [TdP risk drug]." In addition, MSS also identifies therapeutic duplications, drug pairs that are contraindicated by FDA and any drugs that in their labels have recommendations for ECG screening or monitoring during their use.

Once the information provided by MSS has been reviewed and suggestions for management have been considered, the user can record a management plan (Fig. 3, lower right), and then click the "Save" button and click "Report" to generate a pdf file for documentation and for sharing with other members of the healthcare team.

Other applications of MedSafety Scan technology

In April 2020, MSS was released by AZCERT for general use by healthcare professionals treating patients with COVID-19 or conducting research on new COVID-19 therapies. In the first four months, over 3,600 users from 75 countries have registered and created records for over 180,000 clinical cases.

One of MSS's important features is its flexibility which can enable broad application of the technology. AZCERT offers license agreements to commercial entities for custom versions of MSS that are tailored to their specific needs. For example, MSS can

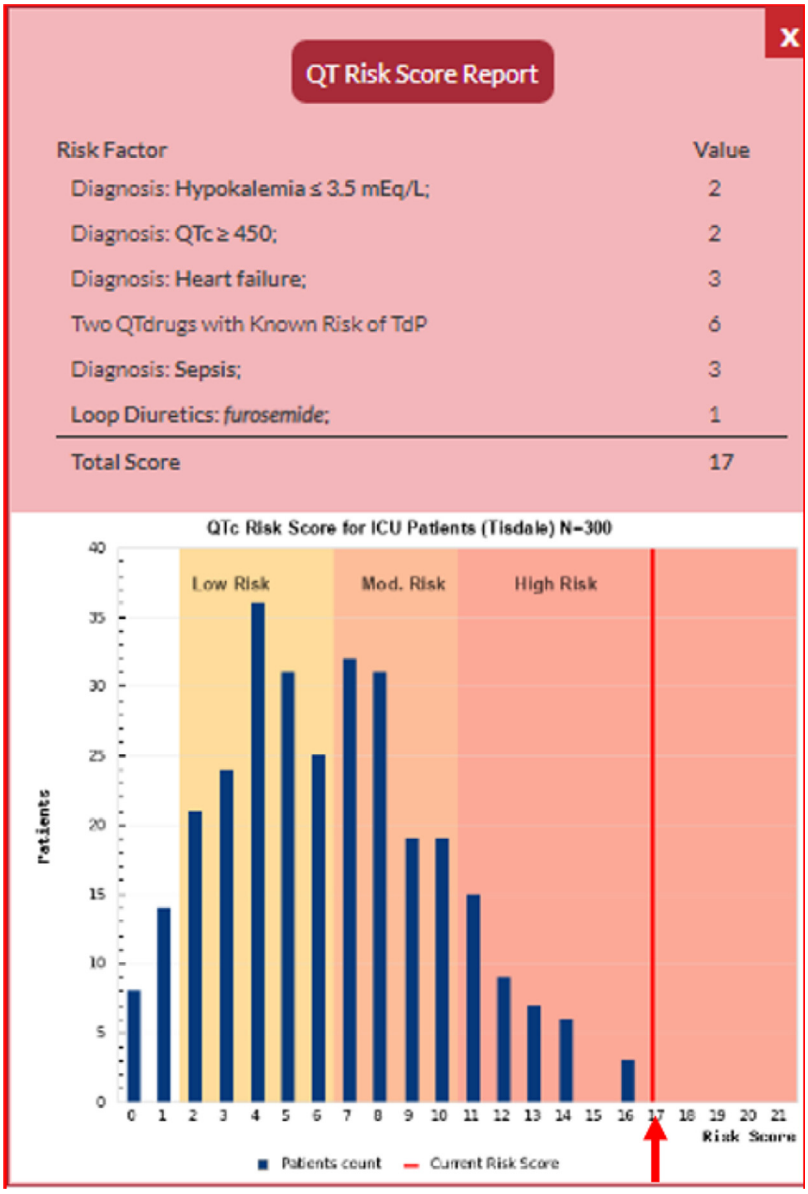

Fig. 4. Screenshot taken after selecting "Details" for a patient's Tisdale QT risk score and that score's ranking (red arrow) in a typical distribution of scores for 300 ICU patients reported by Tisdale et al. (25) (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3.
Severity scale for drug–drug interactions (DDIs)

Severity level 8–10 – Interactions that are considered potentially life-threatening or identified as "Serious" by the Centers for Medicare and Medicaid Services (CMS)
Severity level 4–7 – Interactions that are likely to alter drug response and/or drug exposure and thereby increase the incidence of non-life-threatening adverse events or interfere with therapeutic response
Severity level 1–3 – Interactions mentioned in the drugs' label as potentially clinically relevant but not life-threatening

be customized for use by clinical investigators to support a clinical research protocol and issue alerts that prevent protocol violations. MedSafety Scan is designed for maximum interoperability and AZCERT is committed to working with organizations interested in imbedding MSS in their health IT systems so it can be critically evaluated for its functionality and the ability to improve health outcomes. Also, healthcare organizations wishing to analyze very large files of administrative data for tens of thousands of patients can obtain a license that includes MSS technical assistance and enables batch analyses to identify high-risk patients for possible intervention by their case managers and/or care providers. Use of MSS in collaborative research projects is encouraged by AZCERT and those interested can reach AZCERT by email at info@azcert.org.

Conclusions

The number and complexity of prescription drugs available to practicing healthcare providers have grown steadily and, in response, information technology has developed new systems and software to assist clinicians in managing the overwhelming amounts of medical information. Assisted prescribing, available through the use of clinical decision support, is becoming broadly

available and, if it is to have maximum acceptance and impact, it will require both input and guidance in its design, development and testing from prescribers.

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