

ePrescribing

Summary

- There is now a growing body of data indicating the high incidence of medication errors that occur in a range of clinical settings; whilst the majority of these errors are relatively minor, some will translate into morbidity and, in a minority of cases, death. Many of these errors are now believed to be preventable.
- A variety of ePrescribing systems have been developed as information technology-enabled responses to minimising of the risk of prescribing-related harm and/or improving the organisational efficiency of healthcare practices in relation to prescribing.
- These ePrescribing initiatives range from support for prescribers on placing medication orders and prescribing decision to the broader more visionary perspectives of cross-organisational integration often advocated in key policy documents. As technology has advanced, the scope of ePrescribing has also expanded and charting the evolution of definitions shows the emergence of a progressively more complex picture. In essence, however, this term embraces both the simpler computerised physician (or provider) order entry systems and the more sophisticated computerised decision support system functionality.
- There is evidence that practitioner performance and surrogate prescribing outcomes can be improved through ePrescribing. Positive evidence on safer prescribing outcomes has tended to be reported in the more recent studies. However, overall the evidence showing improved prescribing safety has not been shown to lead to reduced patient morbidity and/or death.
- Evidence of benefits from ePrescribing applications has in the main been derived from evaluations of “home-grown” applications from a few centres of excellence in the United States. Most applications in use are, however, commercially procured and typically lack the sophistication of the more tailored home-grown systems.

Summary continued...

- Poorly designed applications and a failure to appreciate the organisational implications associated with their introduction may introduce unexpected new risks to patient safety and the evidence from evaluations of these home-grown systems is therefore not easily transferable to settings implementing commercial systems.
- The persistent high rates of over-riding of alerts generated by the more advanced ePrescribing systems remains a major concern; finding ways of increasing the sensitivity and perceived relevance of alerts is a major issue that warrants further investigation.
- This will, amongst other things, necessitate undertaking detailed medico-legal work to more accurately quantify the risks to system developers of changing from the current defensive practice in which they take a “belts and braces” approach to generating warnings to one in which there is more selective warning of major risks.
- There is also a need to investigate—in a few carefully selected contexts—the role of “hard-stop” restrictions, which prevent the over-riding of alerts.
- Given that electronic health record systems are now being introduced into NHS hospitals in England, there is a need to consider introducing ePrescribing systems, preferably in an evaluative context that allows the effectiveness and cost-effectiveness of these new systems to be established.

10.1 Introduction

There is now a considerable body of evidence demonstrating that prescribing errors are common and that these are responsible for considerable—potentially avoidable—patient morbidity and mortality.^{1 2} For example, recent UK data indicate that medication-related harm is frequently implicated in admission to hospitals³ and furthermore that an estimated one in seven hospitalised patients experience one or more episodes of prescribing-related harm.⁴ Many studies have now demonstrated

that a large proportion of these adverse drug reactions (ADRs) are potentially preventable.^{5 6}

Given the vast array of drugs now available and the considerable scope for their interaction with aspects of the patients' history and/or other co-prescribed treatments, it is simply no longer feasible for clinicians to know about, retain and judiciously draw on all such information from memory. Electronic prescribing (henceforth referred to as "ePrescribing") has the potential to support professionals by helping them to identify and select potentially appropriate treatments and doses, and also by using patient specific and other local data to guide treatment decisions. In this chapter, we review the potential and empirically demonstrated benefits and risks associated with ePrescribing, building on the more generic discussions on computerised decision support systems (CDSS) in Chapter 8. A more focused critique of the literature on the potential of information technology (IT) to support prescribing in two exemplary particularly high risk contexts (i.e. the use of oral anticoagulants in primary care and approaches to minimising risk of repeat drug allergy in hospitals) is presented in the case studies in the following two chapters.

10.2 Definition, description and scope for use

10.2.1 Definition

There is no agreed definition of ePrescribing. For example, Dobrev et al. have defined ePrescribing as *"the use of computing devices to enter, modify, review, and output or communicate drug prescriptions"*.⁷ In contrast, the definition used by NHS Connecting for Health (NHS CFH) is somewhat broader, including aspects of the governance of prescribing decisions i.e. *"utilisation of electronic systems to facilitate and enhance the communication of a prescription or medicine order, aiding the choice, administration and supply of a medicine through knowledge and decision support and providing a robust audit trail for the entire medicines use process"*.⁸ This definition embraces the use of technology to support the whole process of medication management and it also implies the integration of medication systems with existing electronic health record (EHR) systems (see Chapter 3). The taxonomy of ePrescribing systems proposed by Dobrev et al. emphasises the importance of integration with EHRs (see Figure 10.1).⁷

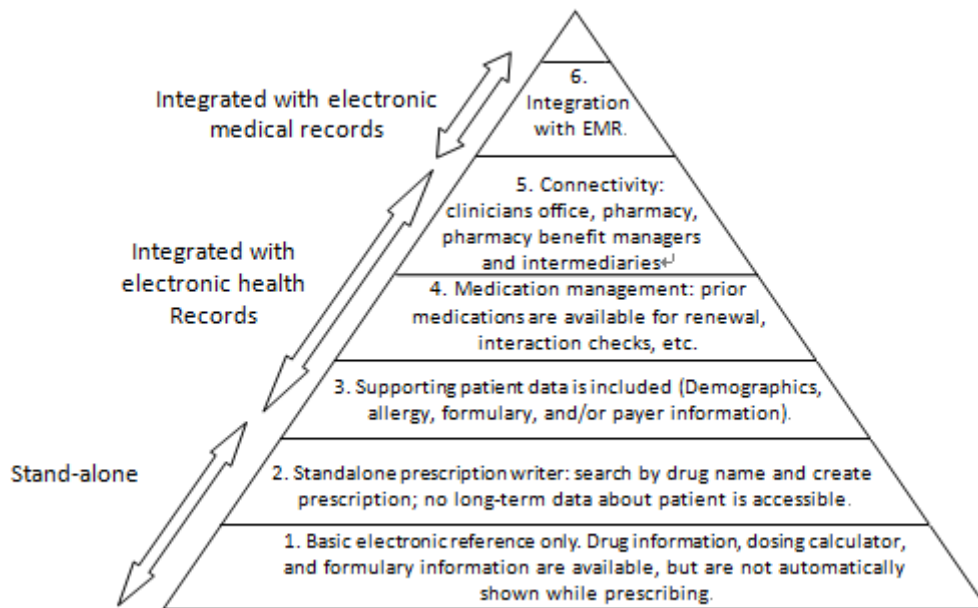


Figure 10.1. The level of sophistication of ePrescribing systems. Modified based on “eHealth Initiative” (2004)⁹ from Dobrev et al. (2008)⁷ (permission to reproduce applied for)

Also of relevance is the degree of support that prescribers are offered. Many of the initially developed systems were, for example, computerised physician (or provider) order entry (CPOE) systems that provided clinicians with drop-down menus to support the prescribing decisions that were being made. More recently, however, the focus of developers has been to build on this basic prescribing support and offer prescribers functionality that takes into account other relevant contextual information about the patient using in-built decision support (see Chapter 8 for a more general discussion about computerised decision support systems (CDSSs)). Table 8.1 provides a framework for considering the degree of decision support offered. It should be noted that both CPOE and CDSS can be used in other contexts, in particular the ordering of investigations; these other uses will not however be considered further in the context of this chapter.

Level 1	Standalone electronic prescription writer or CPOE
Level 2	Electronic drug reference manual
Level 3	Electronic prescription writing and electronic transmission of prescriptions—connectivity to dispensing site
Level 4	Patient specific prescription creation or refilling
Level 5	Basic decision support functionality (integrated or interfaced)— dosage (default and frequencies) and formulary support
Level 6	Drug management—access to electronic medication administration record (eMAR) checks for allergies, drug interactions and duplicate therapies
Level 7	Integration with an EHR
Level 8	Integration with EHR <i>and</i> other clinical information systems (radiology, laboratory and pharmacy information systems)
Level 9	Advanced decision support functionality (integrated or interfaced): adjusting dosages in light of patient characteristics (e.g. ethnicity), physiologic status (e.g. uraemia) and co-morbidities; other medications currently being taken; previous response to the drug, single, daily and life dose limits

Table 10.1
Levels of system sophistication

s t i c a t i o n

Adapted from: Electronic Prescribing: Towards Maximum Value and Rapid Adoption¹⁰ and Kuperman et al.¹¹ (permission to reproduce applied for)

As is evident from the above discussion, the term “ePrescribing” thus encompasses a wide range of systems, these including both CPOE and CDSS and varying degrees of integration with other electronic record systems. In the absence of any agreed definition, ePrescribing is used in this chapter as an inclusive term referring to at minimum the electronic generation of prescriptions, but which may include point-of-care (POC) decision support and, amongst other things, electronic communication of the prescription information to other professionals and agencies involved with medicines management.

10.2.2 Description of use

Prescribing is a complex organisational practice, including a range of processes spread across locations and involving diverse actors, so it is unsurprising that that ePrescribing systems are also organisationally complex; the choices available in their implementation and dimensions that can be included in their evaluation are hence also multifarious. Figure 10.2 depicts the complexity of ePrescribing processes. It shows how ePrescribing can involve different healthcare professionals

at different points of prescribing procedures and how these may require professionals to have access to patients' healthcare or medical records to prescribe appropriately. Medication errors can occur at any point in the prescribing processes i.e. prescribing, transmitting the order, dispensing, administration and monitoring, and ePrescribing systems can therefore potentially support any of these functions.¹²

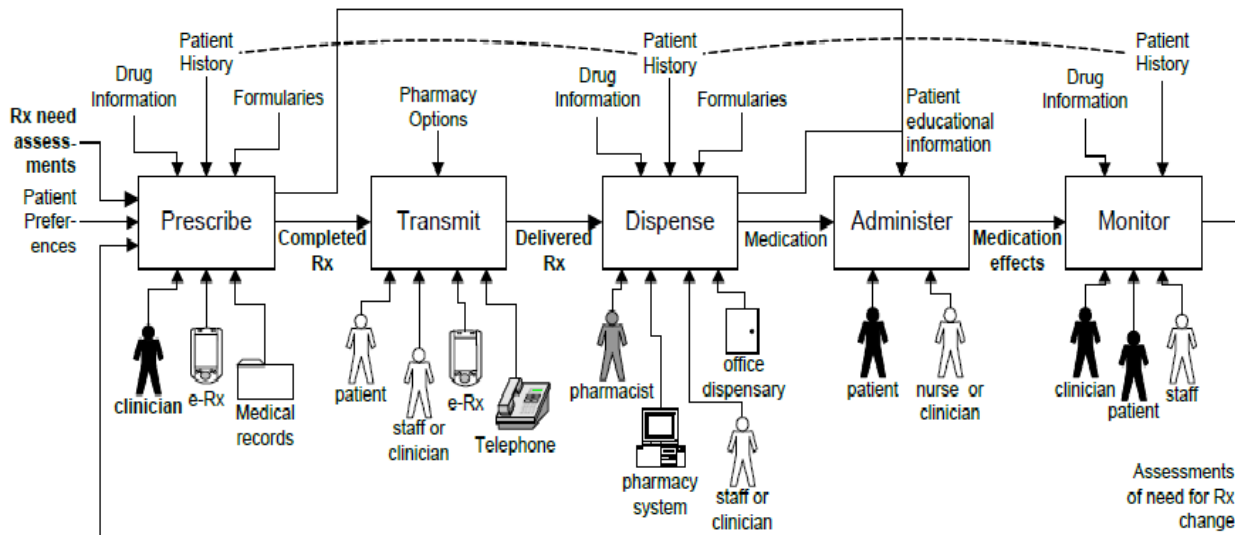


Figure 10.2 High-level ePrescribing architecture

Source: Bell et al.¹³ (permission to reproduce applied for)

ePrescribing systems have been developed for use in a range of healthcare settings, these ranging from primary care to hospital-based care. This issue of setting of use is emphasised in the taxonomy developed by Cornford et al.¹⁴ i.e.:

- Pharmacy-based systems
- Clinical specialty-based systems (e.g. those used in oncology, renal medicine and intensive care)
- Components or modules of larger hospital information system packages
- Home-grown software.

This framework also points to the importance of the genealogy of the system i.e. whether it is home-grown or commercially procured, this also having been highlighted by several other experts (discussed below).

The term ePrescribing may therefore include systems with a range of functions and implemented in a wide range of organisational contexts. When critically reviewing the evidence on the impacts of ePrescribing systems it is important to be sensitive to this variation, as the benefits and risks may be influenced by the system functionality and implementation context. By treating all implementations as being commensurate and aggregating evidence across heterogeneous systems there is a risk that significant insights into system design and implementation will be overlooked.

It follows from the discussion above that there are four dimensions that particularly need to be considered:

1. Interoperability (stand-alone vs. integrated with other health information systems)
2. Functionality (CPOE vs. CDSS-based)
3. The degree of customisation (home grown vs. commercially procured)
4. Setting of use (e.g. primary care vs. secondary care).

These four dimensions are depicted in Figure 10.3.

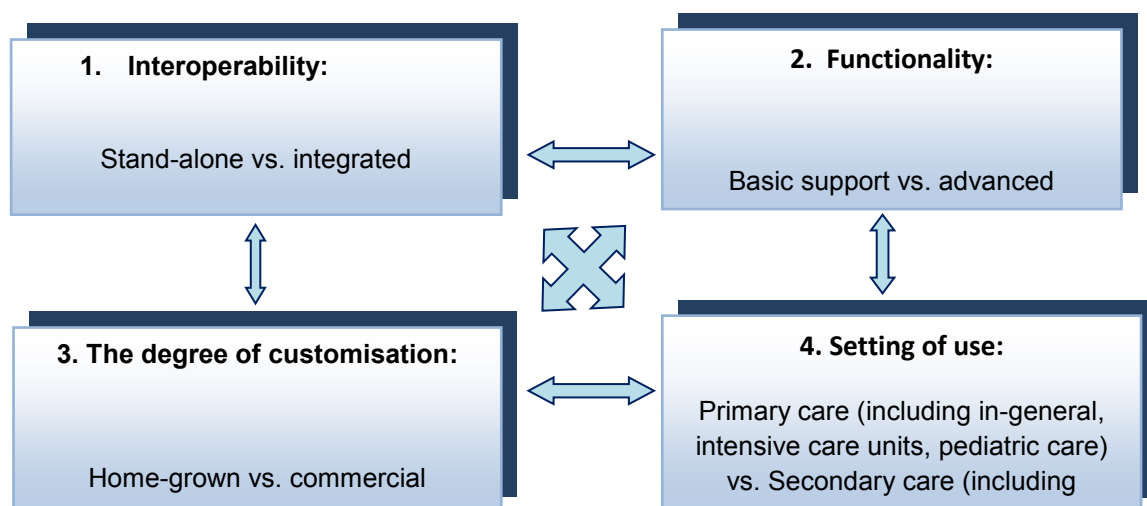


Figure 10.3 Four dimensional taxonomy of technological aspects of ePrescribing systems to understand local implementation landscape

Dimension 1: Degree of inter-operability and integration

This refers to the degree of integration of ePrescribing systems into other healthcare information technologies such as EHRs. ePrescribing systems may be modules within integrated IT systems, linking them to other functional systems, including patient records, accounting systems or inventory systems, or they may be stand-alone systems, with little or no integration with the data held on other systems. Some studies suggest that increasing integration with other systems is likely to be associated with the realisation of greater operational and other benefits.^{15 16}

Dimension 2: Degree of decision support

This relates to the extent of decision-making support embedded in the systems. An ePrescribing system may simply automate aspects of the pre-existing paper-based system, but ePrescribing systems can also alert prescribers and pharmacists to prescribing decisions that break rules embodied in the systems. The categorisation of tiers of alerts fired, whether the alerts warn or block decisions, the rule-setting for alert messages, the extent to which decision support rules draw on individual patient records and the creation of knowledge-bases for prescription, may vary across countries, healthcare organisations, specialities and indeed clinical teams. Contextual factors, such as patients' health care records, drug of medical history, ethnicity, sex, age, weight and local agreements (as embodied for example in practice or hospital-based formularies) add further complexity to the decision making

of clinicians. The growing functional complexity of ePrescribing systems is therefore likely to be correlated with their increasing integration with EHR and other local information systems.

Dimension 3: System development

This refers to the genealogy of the ePrescribing platform—i.e. whether it is a bespoke locally developed (or “home-grown”) system or a standardised commercial package. Locally developed systems may, once mature, demonstrate increased benefits because the systems are developed to fit with idiosyncratic working practices and also because clinicians tend to be more tolerant of the shortcomings of a system that they have, even in a small way, contributed to the development of. However, due to the cost of maintaining local IT development resources and the cost of developing bespoke solutions, the trend across the IT sector has moved away from bespoke development and become more dependent on standardised packages from major commercial suppliers. This axis is a continuum because systems may initially have been developed for local implementation, but their kernel then forms the basis for a commercial package that is sold onto users elsewhere. This is often witnessed in the major software development processes (see Box 10.1 as an example of this).¹⁷ Furthermore, this is so because commercial systems allow differing degrees of configurability, ranging from none or very little to substantial. Rothschild points out the limitation this creates in the current ePrescribing literature¹⁸ as there is possible limited generalisability of findings from studies focusing on locally developed ePrescribing systems, rather than “off-the-shelf” commercial projects that are more commonly found in non-research settings.¹⁹ Most early adopted ePrescribing systems were home-grown while commercial systems tend to be seen as more rigid and lacking the adoptability to meet individual organisational needs.

Box 10.1 Biography of a hospital ePrescribing system: evolution from bespoke system to commercial package

The Prescribing Information and Communication System (PICS) is a portable rules-based CDSS developed by staff at the University Hospitals Birmingham NHS Foundation Trust and is now available on the market following an implementation partnership agreement with CSE Healthcare systems. It is currently used for in-patients, but is being developed for outpatient and ambulatory care settings.

PICS provides ePrescribing and medication functions supported by various patient management services, including laboratory/radiology ordering and results reporting.

Dimension 4: Setting

The setting of deployment can have obvious consequences in relation to the types and frequencies of errors that might be avoided. Systems may, for example, be implemented in small-scale organisational settings such as a single general practice or a ward or intensive care unit or may be implemented across a group of care providers in, for example, a geographical region. The more grand-scale plans for ultimate national coverage across both primary and secondary care settings envisioned by the National Programme for Information Technology (NPfIT) (see Chapter 3) is in many ways unique.

These four factors—i.e. “stand-alone vs. integrated”, “basic vs. advanced”, “home-grown vs. commercial” and “setting”—mutually shape the ways in which ePrescribing systems are implemented and appropriated, and this in turn may affect the quality, safety and efficiency of care. As will be clear from the discussion above, these

dimensions are not necessarily mutually exclusive (see, for example, the description in Box 10.1), nonetheless examining the systematic review papers through the lens of this four-axis typology is potentially useful as it can help to interpret the at-times conflicting body of evidence.

10.2.3 Scope for use

Accurately estimating the incidence of prescribing errors is complicated by the various definitions used and also by a range of approaches to detect and measure errors. More importantly, however, there is a need to appreciate the degree of harm that these result in, this being particularly relevant given the repeated observation that many errors are relatively minor and do not necessarily translate into patient harm. A key question therefore is whether ePrescribing systems can improve the safety of care by reducing risk of errors that are particularly associated with risk of avoidable harm. If so, there are then related important follow-on questions of whether any particular type of ePrescribing system (see discussion above) is any more effective or cost-effective than the other types.

Medication errors are now known to occur at any point in the medicines management process. As discussed above, depending on the type of ePrescribing system used, any of these prescribing functions may to varying degrees be supported by the technology. Medication prescribing and administration are however the two areas of the delivery process with the highest incidence of error and ePrescribing systems are thus potentially particularly effective in supporting the task of generating and issuing prescriptions (see also Chapter 8 and Bates et al.²⁰).

Prescribing of medication is a high volume and high cost activity, with costs of medication in the same group sometimes varying several-fold. There are hence considerable cost savings to be achieved by equipping prescribers with relevant information about the effectiveness, costs and relative cost-effectiveness of different medications, hence this is another important potential use of ePrescribing systems.

In the UK context, ePrescribing systems of varying degrees of sophistication are now routinely used throughout primary care. A key question therefore is to establish whether their use should be extended into hospital in- and out-patient settings.

10.3 Theoretical benefits and risks

10.3.1 Benefits

Quality of care

The two generic domains of eHealth that are in theory supported by ePrescribing are the storing and managing of data, this support being provided irrespective of the level of functionality of the ePrescribing system, and the informing and supporting of decisions when applications have decision support capabilities (see Chapter 4). Box 10.3 details the range of potential benefits associated with ePrescribing systems. A number of more specific claims are made by NHS CFH on their website.²¹

Box 10.3 Main potential benefits of ePrescribing applications on healthcare quality

Potential benefits to patients/carers:

- Reduced under- and over-prescribing

Professionals:

- Standardisation of prescribing practices via the provision of guidelines
- Improved communication amongst prescribers and dispensers (e.g. call back queries, instant reporting that item is out of stock, alerts for unfilled, prescriptions or those that have not been renewed)
- Instant provision of information about formulary-based drug coverage including on-formulary alternatives and co-pay information
- Data available for immediate analysis including post-marketing reporting, drug utilisation review, etc

Healthcare systems/organisations:

- Reduction in lost orders
- Shorter process turn-around time such as the transit time to dispensing

Patient safety

Although healthcare quality and patient safety are inextricably inter-linked (see Chapter 4), much of the premise underpinning the use of ePrescribing relates in particular to improving the safety of medicines management. Errors related to medicines management are probably the most prevalent type of medical error in both primary and secondary care within the UK. Of all types of medicines management errors—prescribing, dispensing, administration, monitoring, repeat prescribing—errors in prescribing decisions are typically the most serious.²⁰

ePrescribing applications should facilitate improved communication between healthcare providers, patient identification, and improved decision and safety support. Improved communication is an inherent benefit of ePrescribing. Improved identification is on the other hand dependent on whether the system is integrated with other clinical information systems such as an EHR (see Chapter 6). Improved decision and safety support is in turn dependent on how alerts are configured and whether decision support is integrated (see Chapter 8); again, the degree to which this is improved is also likely to be dependent on integration with other clinical information systems.

Most notably, ePrescribing has the potential to improve patient safety by decreasing errors in prescribing, monitoring and repeat prescribing. The reduction in these types of errors is clearly potentially dependent on the level of system sophistication, i.e. the degree to which the system is integrated with patient data and decision tools such as drug ontologies and the degree to which it is configured (customised) to the needs of individual prescribers.

Table 10.1 (above) provides a schematic framework of the extent to which different applications are likely to improve prescribing safety. The types of drug errors potentially mitigated relative to the level of ePrescribing applications' sophistication include:

- **Miscommunication of drug orders:** due to poor handwriting, confusion between drugs with similar names, misuse of zeroes and decimal points, confusion of metric and other dosing units and inappropriate abbreviations (Levels 1, 2, 3 and 7)

- **Inappropriate drug(s) selection:** due to incomplete patient data such as contraindications, drug interactions, known allergies, current and previous diagnoses, current and previous therapies, test results etc (Levels 4, 5, 6, 8 and 9)
- **Miscalculation of drug dosage:** incorrect selection of route of administration; mistakes with frequency or infusion rate (Levels 2 and 5)
- **Out-of-date drug information:** for example, in references to alerts, warnings etc or information on newly approved drugs (Levels 2 and 6)
- **Monitoring failures:** results of laboratory test monitoring and drug administration monitoring not being taken into account (Levels 6, 7 and 9)
- **Inappropriate drug(s) selection:** due to clinical incompetence (Level 9).

The use of ePrescribing facilitates identification of the prescribing clinician and the date of prescription thereby allowing quality control measures to be targeted at specific clinicians. It is also possible to configure a system so that it will not process certain orders that are considered dangerous, for instance the accidental prescribing of oral methotrexate for daily use when the intended prescription is for weekly use.²² Additionally, the applications are capable of linking to other clinical information systems for ADE monitoring and reporting²³ and electronic-based representations of prescriptions can form the basis for additional safety measures related to dispensing and administration errors (e.g. automatic dispensing machines and bar-coding of drugs to ensure that patients receive the ordered drug in the correct dose at the specified time; see Chapter 12 for a fuller discussion of this issue in relation to approaches to minimise the risk of recurrent drug allergy).

Improved efficiency

The more integrated systems should also in theory offer advantages in relation to the provision of drawing on data from a variety of sources and hence offer the potential for more advanced decision support functionality; they may furthermore also increase the efficiency of prescribing by, for example, reducing time to dispensing through better end-to-end communication in hospitals between wards and pharmacy.

10.3.2 Risks

Patient safety

How is the safety of these applications ensured? In the United States (US), the Food and Drug Administration (FDA) has classified medical software as a medical device since 1976 and therefore requires proof of software verification by demonstrating consistency, completeness and correctness of the software at each stage of the development life cycle. For the following three types of medical software, proof of software validation is also determined by the correctness of the final software product with respect to the users' needs and requirements:²⁴

- Software as an accessory
- Software as a component or part
- Stand-alone software.

ePrescribing software is however exempted if it is '*...intended to involve competent human intervention before any impact on human health occurs*'.²⁴ In the UK, the Medicines and Healthcare Products Regulatory Agency (MHRA; the UK FDA equivalent) does not consider medical software to be a medical device and therefore does not undertake quality assurance activities. In recognition of this regulative deficit, NHS CFH created a mechanism based on other safety critical software industries' guidance for medical software products. This quality assessment and assurance however only applies to products developed for NHS CFH and no regulatory paradigm exists in either the US or the UK for commercially available medical software products, these being excluded by the "competent human intervention" clause.

This issue is important because although the use of ePrescribing applications for the ordering of drugs should in theory reduce the burden of some types of drug errors, these applications might also introduce new errors. These errors in system design and oversights in development might lead to:²⁵

- Incorrect decision support provided → incorrect medicines ordered and administered → e-latrogenesis.

Theoretically, risks to patient safety by ePrescribing applications could occur at any point in the use of applications due to errors made by the end-user, such as:

- Incorrect patient data input → incorrect decision support → incorrect medicines ordered and administered → e-latrogenesis
- Incorrect orders selected → incorrect medicines ordered and administered → e-latrogenesis
- Incorrect patient selected → inappropriate medicines ordered and administered → e-latrogenesis.

Dependence on the support provided by the application can furthermore put patients' safety at risk when support is not available as, for example, when general practitioners (GPs) prescribe in the context of home visits or hospital doctors change practices or hospitals. Similarly, not understanding the nature of the support provided, such as its limitations, can lead prescribers to misjudge the robustness of the support provided. In contrast, ignoring the advice generated may also threaten patient safety.

Organisational inefficiency

Although the use of ePrescribing is intended to improve the quality of healthcare processes by reducing complexity, the complexity of care often increases as a result of the incorporation of technology into health service delivery. This is primarily due to the significant process changes associated with ePrescribing implementation. Implementing ePrescribing applications may therefore inadvertently impact on the efficiency of care by, for example, resulting in:²⁶

- New or additional work
- New training needs
- Negative emotions/perceptions
- Unwelcome changes to workflows
- Parallel use of electronic and paper-based systems
- Changes in relationships and/or power dynamics
- Time-inefficiencies
- Costs.

10.4 Empirically demonstrated benefits and risks

We identified 30^{15 18 27-54} systematic reviews (SR) on the benefits and risks associated with ePrescribing systems. A detailed description of these studies is presented in Appendices 4 and 5; here we consider the over-riding messages to emerge from this body of work.

As an overview of the SR study, evidence on patient outcomes by ePrescribing has been reported by some of the SRs,^{15 18 27 30 32 33 37 41 42 50-53} but not all of them. Therefore, the evidence on reported impacts on patient outcomes is limited. For example, no impact on mortality was reported in any included study, but there are some studies demonstrating a limited impact on actual ADEs. A greater effect on potential ADEs and/or serious medication errors (MEs) is reported by many of the SR studies.^{30 33 34 37 38 41 46 48 51 52 54} Some SR studies^{32 35 36 39 46 48} reported projected cost savings from ePrescribing by extrapolating from the reductions in MEs, prescription dosages and patients' hospital stays through the use of ePrescribing, but no evidence of direct cost-effectiveness was presented. Furthermore, the majority of studies used weak experimental designs which expose them to the risk of bias.

10.4.1 Empirically demonstrated benefits

Many of these reviews focused on CPOE and CDSS supporting prescribing.^{15 18 27 30 32-36 41 46 48 53} Some of the SRs focused on CDSS for prescription.^{37 38 49-51 54} We detail most reviews below, omitting those where there is duplication of studies (and conclusions) with other reviews discussed either here or in Chapter 8 on CDSS.

Impact on patient safety: mortality, morbidity and surrogate marker of medication errors

Sub-standard prescribing practices, such as inappropriate drug selection due to allergies or contraindications and incorrect dosing, are frequently evaluated outcomes. Differences in the way errors are defined and measured make generalising across organisational settings difficult. For example, Classen and Metzger, citing Nebeker et al., write that:⁵⁵

'One of the ongoing controversies in medication safety is how to measure the safety of the medication system reliably and how to assess the effect of interventions designed to improve the safety of medication use. Clearly, common nomenclature, definitions, and an overall taxonomy for medication safety are essential to this undertaking and the lack thereof has significantly hampered the comparison of various medication safety interventions among different centres.⁵⁶ At the heart of an even more fundamental controversy is whether the focus of patient safety should be on errors or adverse events as a means of assessing and improving the safety of the healthcare system.'

Several SR papers^{18 27 32 48 53} demonstrated limited evidence on the reduction of ADEs through the use of ePrescribing systems. For example, Wolfstadt, et al.⁵³ conducted a SR evaluating ten studies to examine the effect of CPOE with CDSS functionality on a range of ADEs in a range of clinical settings and found that half of the studies found a significant reduction in ADEs. None of the studies however employed randomised controlled trial (RCT) designs, and seven of the 10 studies evaluated home-grown systems. The weak study designs and heterogeneity of patient settings, outcome measures and system genealogies precluded any definitive overall conclusion on effectiveness. There was no discernible impact on other important outcomes such as death.

The SR of 27 studies by Ammenweth et al.²⁷ highlighted the complexity of interpreting this body of evidence. This SR, which reported at about the same time, included studies evaluating CPOE systems both without and with CDSS of varying degrees of complexity. The authors included studies that employed controlled and before-after designs undertaken in a range of in-patient settings and evaluating both home-grown and commercial systems. Overall, this evidence showed that 23/25 studies reported reduced rates of medication errors, the effect size ranging from 13-99%. Furthermore, six of the eight studies reporting on potential ADEs found a reduction in the incidence of this outcome (effect size 35-98%). More importantly, two-thirds of the six studies reporting an actual ADE also found a significant reduction of similar size magnitude for potential ADEs. Expressed in another way, however, only four of these 27 studies—which employed study designs that rendered

it difficult to, in the authors' words, '*exclude a major source of bias*' –found a positive impact on clinical endpoints. To their credit, however, the authors undertook a range of subgroup analysis on the "ME" surrogate outcome: this revealed that systems that were home grown and had advanced CDSS functionality were more likely to be effective than commercial and basic CPOE systems. There was, however, no detectable differences by population studied, inpatient setting or study design.

Clamp and Keen³² conducted a SR in which they included 70 studies on healthcare IT systems with variable designs in a range of settings including general medical, surgical, intensive care, paediatric, tertiary, acute and subspecialty renal care settings. Twenty-seven of these studies were concerned with the evaluation of CPOE systems. Although there is no strong evidence that CPOE reduces preventable ADE rate, one study reported decrease in preventable ADEs of 17%⁵⁷ while another study showed one ADE would be prevented every 64 days by the use of CPOE in a paediatric unit, but there was no reporting of statistical significance.⁵⁸ They also concluded that all MEs were reduced significantly by the use of COPE by 40-80% with a significant decrease in serious MEs by 55%⁵⁷ and non-serious MEs by 86%.⁵⁹

Rothschild¹⁸ also assessed ePrescribing in critical care, general inpatient and paediatric care settings. Their review of 18 publications reported improvements in a range of process and surrogate markers. Three studies, two of which^{57 59} have been already presented in the review by Clamp and Keen, reported that the incidence of serious MEs/ADEs were significantly reduced by the use of CPOE, but the same effect was not identified in pediatric ICU study.⁶⁰

Shekelle et al.⁴⁸ conducted a SR study on the evaluation of costs and benefits of health IT mainly in US outpatient and inpatient paediatric settings, and in so doing identified 30 studies in relation to CPOE. The review showed consistent evidence that CPOE with CDSS has significant potential to reduce harmful MEs, particularly in inpatient paediatric and neonatal intensive care settings. Mullett et al.⁶¹ found that ePrescribing with CDSSs decreased pharmacist interventions for erroneous drug doses by 59%. CPOE (which is not combined with CDSS) was found to be effective in reducing medication dosing errors. Potts et al. conducted a prospective cohort

study to examine medication prescribing errors and potential ADEs before and after implementation of a home-grown CPOE system in a paediatric intensive care unit. They found that the use of home-grown CPOE significantly reduced both MEs (30.1 to 90.2 %, $p < 0.001$) and potential ADEs (2.2 to 1.3%, $p < 0.001$).⁵⁸

There are other SR studies which address the effect of COPE on serious in medication errors regarding safety, but apart from the above four studies, most of the studies failed to provide the evidence on ADEs or a few can provide the effect with low statistical power. For example, in a variety of settings with different types of patient populations, Shamliyan et al.⁴⁷ systematically studied 12 studies in in-patient settings ranging from adult primary care, acute care to paediatric/ newborn intensive care unit settings. The review shows that prescribing errors amongst the majority of the studies (8/10 studies) while they also showed a significant reduction in doing errors (3/7 studies) and in ADEs (3/8 studies), compared with handwritten orders. It also reported that one RCT and 5 uncontrolled interventions and four observational studies demonstrated that the implementation of CPOE is associated with the reduction of medication errors in both adults and paediatric patients without providing quantitative estimation of relative risk. Three studies also suggested that the implementation of CPOE systems had a positive impact on reducing ADEs, but without providing clear statistical evidence in support of this conclusion. For example, one study showed that the use of “CPOE would prevent 9 ADEs per 1,000 prescriptions in paediatric”⁵⁸ populations while another study showed that “12 ADEs per 1,000 prescriptions in adult population” could be prevented.⁶² On the reduction in prescribing errors, the evidence shows that CPOE was associated with a 66% reduction in adults with odds ratio [OR] =0.34; 95%CI 0.22, 0.52 and a positive tendency in children (P for interaction =0.028).

From their wider review of 30 CPOE studies conducted in out-patient settings, Eslami et al. identified four studies evaluating the effect of ePrescribing on drug safety;³⁵ all four systems had in-built CDSS functionality, but none of these four studies demonstrated any significant improvement in ADEs; the potential reasons for this may have varied across studies including non-use of systems and a small number of events and associated low power. Eslami et al. concluded that ‘...*in spite of the cited merits of enhancing safety published evaluation studies do not provide*

*adequate evidence that ePrescribing applications provide these benefits in outpatient settings*³⁵.

Hider systematically reviewed the effectiveness of ePrescribing to improve practitioner performance and patient outcomes by covering 52 studies in a range of settings, including primary care, intensive care, inpatient and outpatient settings and most studies reported that CDSS could improve practitioner performance, especially for the prescribing of potentially toxic drugs and that alerts on prescription can reduce ADEs and improve other patient health outcomes including the risk of renal impairment.⁴¹ The inability of some of the studies to find any improvement in health outcomes may be due to the small sample sizes, but the results from a meta-analysis of the studies evaluating electronic dose adjustment found that CDSS can reduce the frequency of adverse reactions and decrease the length of hospital stays.

Schedlbauer et al. conducted a SR in which they identified 20 studies evaluate the impact of alerts on prescribing behaviour.⁴⁶ The authors were found that the majority of alerts resulted in a reduction of MEs, but only a minority of studies reported on clinical outcomes.

Apart from the reduction of ADEs and MEs, some SR papers reported that ePrescribing has shortened the length of patients' hospital stay through more appropriate and effective prescription. For example, the SR study conducted by Durieux et al. assessed the beneficial effects of CPOE with CDSS on the process or outcome of health care with the focus on drug dosage in inpatient and outpatient settings by covering 26 comparisons in 23 articles of majority were RCTs (23 RCTs, 1 CT and 2 CCT).³³ Computerised advice on drug dosage had the effect to increase the initial dose of drug and serum drug concentrations, and this led to a more rapid therapeutic control, the reduction of the risk of toxic drug levels, as a result, shortening the length of patients' hospital stay. Six comparisons reported the length of time spent in hospital. Overall they showed a significant reduction in hospital stay during the computer group (SMD-0.35, 95%CI 0.52, 0.17). In one study a significant reduction in length of stay was found (SMD -0.04, 95%CI -0.07, -0.01, but Durieux et al. query the reliability of the confidence intervals due to a potential unit of analysis error.³³

Eslami et al. conducted a SR study addressing the characteristics of CDSSs for tight glycemic control (TGC) and reviewed their effects on the quality of the TGC process in critically ill patients.³⁴ Most of the CDSSs included in the studies were stand-alone. All of the controlled studies in Eslami et al.'s review reported on at least one quality indicator of the blood, but only one study reported a reduction in the number of hypoglycaemia events.³⁶

Mollon et al. also conducted a SR study of 41 papers to evaluate the features of ePrescription with CDSS for successful implementation, prescribers' behaviours and changes in patient outcomes.¹⁵ The authors identified five studies from 37 (12.2%) "successfully implemented" trials showing improvement in patient outcomes. It is interesting to note that all the five studies showing patient outcome improvements were published after 2005, implying that systems are becoming more effective in mitigating patient outcome risk.

Yourman et al. assessed systematically the improvement of medication prescription in older adults, with the focus on CDSS intervention in outpatient and inpatient settings, mainly in the US.⁵⁴ A majority of the studies were of systems providing direct support at the point of care and were not condition or disease-specific. Of 10 studies testing CDSS interventions for older adults, eight showed at least modest improvements (median number needed to treat, 33) in prescribing, as measured by minimising drugs to avoid, optimising drug dosage, or improving prescribing choices in older adults (according to each study's intervention protocols). The majority of studies reported medication-related process outcomes, for which CDSS generally showed positive effects, including lower rates of prescribing inappropriate drugs and closer adherence to better drug choices or dosages for older persons. The studies reviewed indicate that often straightforward point of care recommendations showed modestly effective results from a process outcomes perspective.

Improved practitioner performance in prescription

Reviews assessing the impact of ePrescribing on the quality of care include studies focusing on the ordering of prophylactic prescriptions, adherence to prescribing

guidelines and organisational efficiency. The definitions and measurement of quality outcomes vary, so generalising across organisational settings is difficult.

Garg et al. included 29 trials of drug dosing and prescribing, with single-drug dosing improving practitioner performance in 15 (62%) of 24 studies; another five applications used electronic order entry for multi-drug prescribing with four of these applications improved practitioner performance.³⁸ Nies et al. however, assessed the same studies included in the review by Garg et al., but came to a different conclusion, namely that '*...drug dosage adjustment was less frequently observed in positive studies (29 per cent) than in negative studies (71 per cent)*'.⁶³ Whilst Nies et al. noted that their conclusions differed to those made by Garg et al. they did interpret why this contradictory finding was made.⁶³ This discrepancy may have resulted from differences in the definition of success, but merits further exploration.

Time efficiency and improved work-flows

One of the important themes for organisational implications of the implementation of ePrescribing systems highlighted in the literature is time efficiency and improved working practices.

Tan, et al. systematically examined whether the use of CDSS has an effect on newborn infants' mortality and morbidity and on healthcare practitioners performance by assessing three RCTs.⁵¹ One study,⁶⁴ which investigated the effects of a database programme in aiding the calculation of neonatal drug dosages found that the length of time for the calculation was significantly reduced among resident paediatric staff, paediatricians and, to a lesser extent, for nurses by the use of the Neodosis spreadsheet program, while the system eliminated serious errors. However, there were insufficient data from the randomised trials to determine the patient benefit or harm from CDSS in neonatal care.

Niazkhani systematically reviewed 51 papers covering 45 studies to evaluate the impact of CPOE on organisational efficiency and, in particular, clinical workflow.⁴⁴ Most of the CPOEs studied were commercial and the majority were in adult inpatient settings in teaching hospitals but also included pediatric settings. The evidence shows that the implementation of CPOE resolved many disadvantages associated

with the work-flow in paper-based processes. For example, 11 studies showed that CPOE systems improved work-flow efficiency by removing many intermediate and time-consuming tasks for healthcare professionals, while six before-after studies showed a substantial decrease in the drug turnaround time, varying from 23-92%. Furthermore, three studies found a significant reduction of 24-69% in the time interval between clinicians' radiology requests and the completion of the procedures pre- and post-implementation. The same three studies also showed that a shorter turnaround time was found for laboratory orders, varying from 21-50%.

Clamp and Keen also noted that although there was no evidence of reduction in pharmacists' time spent dealing with prescriptions, there were changes in their working patterns.³² The authors argued that pharmacists have an important quality control role in checking prescriptions, with one study finding that pharmacists only spent 5-20% of their time on direct clinical care.⁶⁵ Prescription monitoring and adaptation was reduced to less than 10% in a UK hospital using ePrescribing, allowing pharmacists to spend around 70 % of their time on direct patient care.⁶⁶ In a US study the pharmacists spent 46% more time on problem-solving activities and 34% less time filling in prescriptions.⁶⁷ The authors noted that three studies—including one RCT—found that the total time for direct and indirect patient care increased due to the introduction of the ePrescribing system and there was a reduction in pharmacist interventions for prescriptions.⁶⁸⁻⁷⁰ Evidence for improved organisational efficiency was also found by Clamp and Keen in their review of turn-around times.³² Mekhijan et al. found a statistically significant reduction in turn-around times following the implementation of ePrescribing (64% reduction; $P < 0.001$).⁷¹ Turn-around time from ordering to dispensing was found to decrease by up to 2.5 hours in a study by Lehman et al.⁷²

Sintchenko et al. conducted an SR study of 24 papers (RCTs) to assess the importance of the type of clinical decisions and decision-support systems and the severity of patient presentation on the effectiveness of CDSS use in US and Europe.⁵⁰ The study reported that control trials of CDSS indicated greater effectiveness in hospital settings than when applied to chronic care and CDSS improved prescribing practice and outcomes for patients with acute conditions,

although CDSS were effective in changing doctors' performance or outcomes in primary care.

Guideline compliance

Another recurring theme in the literature is guideline compliance. A number of SRs have demonstrated the improved level of adherence to guidelines.^{18 35 36 39 42 49}

This body of evidence suggests that achieving guideline compliance would increase cost effectiveness by reducing unnecessary prescriptions and laboratory tests. For example, Eslami et al.^{35 36} examined adherence to guidelines in outpatient and inpatient settings as part of their systematic reviews of ePrescribing. For outpatient settings, the authors concluded that there is evidence of the ability of ePrescribing applications to increase healthcare professionals adherence to guidelines and hypothesised that cost reduction can be achieved when guidelines are specifically geared towards this goal.³⁵ The authors based their conclusions on 11 studies evaluating the impact of ePrescribing with a CDSS on the adherence to a guideline or another standard. Among these, four studies showed that there was a significant positive effect on adherence;⁷³⁻⁷⁶ two studies showed a positive effect without reporting on statistical significance;^{77 78} and five studies did not find a significant difference between the control and the intervention groups.

Rothschild¹⁸ systematically evaluated the effects of CPOE on clinical and surrogate outcomes in hospitalised patients in both general and critical care settings, covering 18 papers. The review found that several process outcomes improved with CPOE, including increased compliance with evidence-based practices, reductions in unnecessary laboratory tests and cost savings in pharmaco-therapeutics. Guideline compliance (corollary orders) increased from 21.9% to 46.3% (P=0.01), but there was no effect on length of stay.⁷⁹

10.4.2 Empirically demonstrated risks

A main limitation to studies reporting negative consequences associated with the use of ePrescribing is that they tend to not indicate which of the many possible mechanisms might have resulted in the adverse effects.

Impact on patients

Eslami et al. noted that recent studies suggested that errors, ADEs and even mortality may have increased after CPOE implementation.³⁶ Van Rosse et al.⁵² also address the increase in mortality rates associated with the introduction of a CPOE system reported by Han et al.⁸² This study has been discussed extensively in the literature.⁸³⁻⁸⁵ Han et al. describe the most serious of risks to patient safety, mortality.⁸² The authors found that the unadjusted mortality rate increased from three per cent before ePrescribing implementation to seven per cent after ePrescribing implementation ($P < 0.001$). Observed mortality was consistently better than predicted mortality before ePrescribing implementation, but this association did not remain after ePrescribing implementation.⁸² The Han et al. study demonstrated that increased mortality can be associated directly with modifications in standard clinical processes: With the ePrescribing system, order entry was postponed until after the processing of patient admission.⁸⁶ Although accurate patient registration is important to patient safety, delaying care and treatment of severely ill patients due to the new work practices embedded in computer systems may adversely affect patient outcomes.⁸⁷

However, van Rosse et al.⁵² also refer to the study conducted by Del Beccaro et al.⁸³ which evaluated the same CPOE system as Han et al.,⁸² but did not find a significant change in mortality rates. Only three hours of training were conducted during the three months before the implementation day. Ammenwerth et al. compared these studies and noted that there were important differences in design and implementation strategies.⁸⁵ Han et al.⁸² studied CPOE use with a more critically ill and younger patient population than Del Beccaro et al.⁸³ Furthermore, Han et al. studied outcomes only five months after CPOE implementation,⁸² whereas Del Beccaro et al. extended their post-implementation study period to 13 months.⁸³ The longer study period of Del Beccaro et al. may have averaged out a potentially higher error rate in the first few months after CPOE implementation due to a learning curve effect.⁸³ Keene et al.⁸⁴ also studied the effect of CPOE introduction in a critically ill paediatric population with comparable results to those of Del Beccaro et

al.⁸³ The study conducted by Keene et al. suggest that most of the possible factors which led to the increase of mortality after the implementation cannot be attributed to the CPOE system itself, but rather resulted from the implementation process.⁸⁴

Furthermore, Rosenbloom et al. noted that the implementation process for the application described by Han et al. did not incorporate steps or elements known to ensure system dependability and usability.⁸⁶

Bradley et al. has also noted that total error reports increased post-implementation of ePrescribing, but found that the degree of patient harm related to these errors decreased.⁸⁸ Furthermore, Shulman et al.⁶² noted that the proportion of drug errors fell significantly from seven per cent before ePrescribing introduction to five per cent thereafter ($P < 0.05$), but that this occurred against the backdrop of a strong declining linear trend of the proportion of drug errors over time ($P < 0.001$).⁶² These authors, however, reported three important errors intercepted by ePrescribing which could otherwise have resulted in permanent harm or death; these errors were identified and then acted upon by pharmacist or nurse intervention, i.e.:⁶²

'A potentially fatal intercepted error occurred when diamorphine was prescribed electronically using the pull down menus at a dose of seven mg/kg instead of seven mg, which could have lead to a 70-fold overdose. In a separate case, amphotericin 180 mg once daily was prescribed, when liposomal amphotericin was intended. The doses of these two products are not interchangeable and the high dose prescribed would have been nephrotoxic. In the third case, vancomycin was prescribed one g intravenously daily to a patient in renal failure, when the appropriate dose would have been to give one g and then to repeat when the plasma levels fell below 10 mg/L. The dose as prescribed would have lead to nephrotoxicity.'

Koppel et al. conducted a study on drug errors introduced by ePrescribing. The authors '*...identified 22 previously unexplored drug error sources that users reported to be facilitated by ePrescribing through their assessment.*⁸⁹ The sources were grouped as: (1) information errors generated by fragmentation of data and failure to integrate the hospital's several computer and information systems; and (2) human-

machine interface flaws reflecting machine rules that do not correspond to work organisation or usual behaviours.⁸⁹ However, this study, has been criticised due to the high risk of bias with respect to their key findings. In response to this study, Bates, for example, notes that:⁹⁰

'A main limitation of Koppel et al.'s study was that it did not count errors or adverse events, but instead measured only perceptions of errors, which may or may not correlate with actual error rates. Furthermore, it did not count the errors that were prevented. As such, it offers no insight into whether the error rate was higher or lower with ePrescribing. Unfortunately, however, the press interpreted the study as suggesting that ePrescribing increases the drug error rate. While the authors did not state this, a press release put out by the journal that published the article did so.'

Risks to patient safety may arise indirectly from application use. For instance, a survey of UK GPs found that some respondents erroneously believed that their computers would warn them about potential contraindications or if an abnormal dose or frequency had been prescribed, highlighting how lack of knowledge and training in how ePrescribing systems function can compromise patient safety.⁹¹

Risks to patient safety can arise not only from system use but also from a lack of actual usage undermining the ability of ePrescribing applications to confer the envisaged benefits to patient safety. A sub-section of the review by Eslami et al. looked at system usage, the authors noted that there was wide variability in the degree of ePrescribing usage.³⁵ Four studies found that of all prescriptions, 3–90 per cent were entered electronically.^{68 92-94}

The SR by Chaudry³¹ included one study which used a mixed quantitative–qualitative approach to investigate the possible role of such a system in facilitating PEs reported that 22 types of ME risks were found to be facilitated by ePrescribing, relating to two basic causes: fragmentation of data and flaws in user-system interface.⁸⁹

Ammenwerth et al. looked at the relative risk reduction on ME and ADE by CPOE covering 27 studies on ePrescribing mainly in the US in patient care settings with study designs including before-after studies/time-series analysis and two RCTs.²⁷ Twenty-three of these studies showed a significant relative risk reduction for medication errors of 13-99%, but it is also worth highlighting one exceptional study which looked at the implementation of a commercial ePrescribing system with advanced CDSS at two study units between 2002 and 2003 for three months, which reported a significant increase of 26% for the risk of medication errors.⁹⁵

Negative impact on professionals' performance and organisational efficiency

It should be noted that negative impact of ePrescribing systems on healthcare professionals' performance and organisational efficiency can result in risks to patient safety. However, such negative evidence requires careful consideration to identify whether these risks are intrinsic to ePrescribing systems or are a part of the socio-organisational learning processes in the implementation.

Eslami et al.³⁵ and Eslami et al.³⁶ conducted SR studies to evaluate studies of CPOE with/without CDSS on several outcome measures in outpatient and inpatient settings respectively. In outpatient settings, the authors found three studies^{67 69 96} (one RCT and two non-RCTs) that reported an increase in the total time for direct and indirect patient care due to the implementation of the CPOE system, while three studies (one RCT and two non-RCTs) also reported an increase in ordering time with the introduction of CPOE.⁹⁷⁻⁹⁹ Two of the studies^{96 98} were also assessed by Shekelle et al. who evaluated 30 studies on CPOE as a part of their evaluation of the costs and benefits of health information technologies in various healthcare settings.⁴⁸ The authors noted that two studies reported an increase of the clinicians' time for order entry using CPOE compared to paper methods, and both studies demonstrated that CPOE took up slightly more clinician time.

Poissant et al. reviewed 23 papers on EHRs to evaluate time efficiency of physicians and nurses and identify factors that may explain efficiency differences across studies.⁴⁵ The authors found that the use of central station desktops for CPOE was inefficient, increasing the work time from 98.1% to 328.6% of physician's time per working shift (weighted average of CPOE-oriented studies, 238.4%).

Tierney et al. found that interns in the intervention group spent an average of 33 minutes longer (5.5 minutes per patient) during a 10-hour observation period writing orders than did interns in the control group ($P < 0.001$).⁷⁹ Another BWH study published by Bates et al. using work study techniques found that for both medical and surgical house officers, writing orders on the computer took about twice as long as using the manual method, these differences being both clinically and statistically significant ($P < 0.001$).⁸⁰ However, medical house officers recovered nearly half the lost time due efficiency improvements in other administrative tasks, for example looking for charts.⁸⁰ Additionally, a pilot of ePrescribing standards in the US found that providers noted that '*...everything interacts with everything*' making for an overwhelming amount of alerting and therefore additional work.⁸¹ Other than writing orders, one observational study by Almond in the UK found that the time to complete the ward drug administration rounds doubled for healthcare assistants.⁸²

Niazkhani conducted a SR study of 45 studies in 51 papers to evaluate the impact of CPOE on organisational efficiency, in particular clinical workflow.⁴⁴ The author noted that the implementation of CPOE led to the creation of difficulties in work-flow mainly due to changes in the structure of pre-implementation work and negative evidence was reported on time efficiency. Five studies showed time inefficiency due to the implementation of CPOE and four out of the five studies reported a significant increase in time. The proceduralisation of order entry and the structuring of relationships between actors were also found to be a source of time inefficiency. Difficulties in choreographing the various actors and a reduction in team-wide discussions were also found.

The scope for potential clinician process efficiency gains from the introduction of CPOE will be dependent at least in part on the inefficiency and thoroughness of the previous paper-based processes, combining retrieval, viewing of information, data entry, and in many cases, responses to alerts and reminders. The work practices of nurses have been found to be proceduralised, but clinicians may follow idiosyncratic practices.¹⁰⁰

10.4.3 Implications of technological taxonomy to benefits

We identified some of the SR papers assessed technical functionalities based on the three different types of taxonomy: “commercial versus home-grown” systems,^{27 31 32 44 47 48} “basic versus advanced” CDSS for prescription^{27 30 32 34-36 40 46 47 49 53 54} and “stand-alone versus integrated” systems.^{27 31 32 38 42 49} The evaluation from these perspectives is extremely important to obtain the insight into what kinds of elements make contribution to successful implementation of ePrescribing systems for the improvement of patient safety and organisational efficiency. However, Wier et al.¹⁰⁸ point out how often authors provided little information about the application, technical infrastructure, implementation process or other descriptive data. Such missing information leads to difficulties of obtaining accurate picture of the implementation sites and generalisability of evidence from studies. Bearing these issues in mind, this section demonstrates key evidence of benefits of ePrescribing from the body of literature.

Commercial versus home-grown systems

Not all of the systematic reviews papers evaluated relevant studies from a point of technological taxonomy and the evidence thus tends to be presented without distinguishing between the findings from in-house built and commercial systems. Some of the papers do however provide some insights into findings when viewed through this lens. There are some SRs reporting positive results with home-grown systems^{27 31 32 48} but there is limited evidence reported regarding the benefits of commercial systems with high-quality of studies. However they demonstrate that customising commercial systems to tailor them to local hospital environments can also bring benefits^{27 35 45 47 53}.

Clamp and Keen³² found that there was no overall evidence that use of ePrescribing systems reduces the rate of preventable ADE, but pointed out that one study showed that the internally developed systems, with CDSS of menu of medications, default doses, range of potential doses, limited drug-allergy checking, drug-drug-interaction and drug-laboratory checking significantly reduced serious MEs by 55%⁵⁷ as well as an 86% decrease in dose, frequency, route, substitution and allergies.⁵⁹ The study also found an overall decrease in preventable ADEs of 17%.⁵⁷

Shekelle et al.⁴⁸ also cite a prospective cohort study investigating impact of a “home-grown” CPOE on MEs and ADEs in a paediatric intensive care.⁵⁸ This study found a significant reduction of both MPEs (30.1 to 90.2%, $P < 0.001$) and PADEs (2.2 to 1.3%, $P < 0.001$). Another study by Cordero et al. in neonatal intensive care found that a CPOE system could eliminate gentamicin prescribing errors.¹⁰¹ Also another study which implemented a home-grown CPOE system with advanced CDSS (including allergy alerts, dose checking, drug interaction, clinical pathways, patient and place specific dosage, interfaces with clinical data repository—order related and laboratory alerts) reported the potential reduction of ADE, that is, the prevention of one ADE every 64 days by the use of the ePrescribing system in a paediatric setting but no statistical evidence was provided to support this estimation.⁵⁸

After 2007 some SRs started to report the effect of commercial systems for patient safety in parallel to the studies of home-grown systems.^{27 35 47}

In a recent review, Eslami et al. employed the taxonomy of “basic support” versus “advanced support/alerts” to evaluate the impact of ePrescribing systems on safety; cost and efficiency; adherence to guideline; alerts; time; and satisfaction, usage, and usability in the outpatient setting while it also addressed the “stand-alone” versus “integrated systems” and “commercial” versus “home-grown” dimensions of ePrescribing systems.³⁵ However, the evidence drawn from the study in relation to each dimension are not clearly stated and are obfuscated in the analysis. However, it is worth mentioning one observational study¹⁰² which showed “*important weaknesses in generating alerts in four commonly used commercial systems in Britain’s GP offices*”. Those systems were unable to generate “all 18 predefined established alerts for contraindicated drugs and hazardous drug-drug combinations”.³⁵

Another important literature on this taxonomy is the study by Ammenwearth et al. who conducted a systematic review of 27 papers on ePrescribing implementation mainly in the US outpatient, inpatient and intensive care settings.²⁷ The study included only two RCTs—most of the other studies employed before-after and in some cases time-series designs. The ratio of studies looking at commercial systems vs. home-grown systems was approximately 1: 1, with one study adopting both

designs. Their sub-group analysis of 25 studies comparing reductions in medication errors between home-grown and commercial systems highlighted a greater risk reduction in errors with the home-grown systems. In spite of these reported results, the quality of those studies was not high as many of them did not fully specify the experimental design, did not describe the cohort or state whether the comparison and intervention groups' treatment was commensurate and only two studies were randomised trials.

Setting

Shamliyan et al. reviewed 12 studies published from 1990 to 2005 evaluating the impact of ePrescribing systems on prescribing errors in in-patient settings.⁴⁷ One study⁵⁸ which implemented in-house developed system in a 20-bed paediatric intensive care unit setting with prospective, intervention study found 95.9% of overall errors reduction ($P < 0.05$), 99.4% of total prescribing errors reduction and 88.8% of wrong drug reduction ($P = 0.07$) as absolute change in rate while the study also found 7.6% ($P = 0.69$) of wrong dose increase. Another study¹⁰¹ examined the implementation of a commercial system with a retrospective study in a post-natal intensive care unit setting and found that medication errors to prescribe gentamicin reduction and to prescribe the wrong dose of gentamicin were eliminated, but with no statistical significances provided.

Overall, although definitive evidence from systematic reviews of RCTs comparing home grown and package systems is lacking, the data suggest that home grown systems are more effective than commercial systems in reducing prescribing errors. There is however as yet no clear data available on whether these differences translate into improvements in important patient outcomes such as death.

ePrescribing systems with “basic” vs. “advanced” decision support

Overall picture of the taxonomy of “basic” versus “advanced” CDSS is ePrescribing systems with advanced CDSS showed a higher relative risk reduction compared to those with limited or no decision support.^{46 49} In particular, the evidence in the literature reported that the “patient-specific” alerts improve the quality of prescribing.²⁷ This taxonomy is closely linked to the other one, “stand-alone” versus

“integrated” systems. The following paragraphs refer to the key literature with CDSS elements of “basic” versus “advanced” decision support.

The SR study by Schedlbauer et al. provides important evidence in relation to the typology of DSS/alerting systems and reminding systems in relation to ePrescribing systems.⁴⁶ The study focused on the effects of those alerts and reminders on prescribing behaviour mainly in the US inpatient settings covering the relevant papers published between 1994 and 2007. Twenty studies, which have employed randomised and quasi-experimental designs were included. Categories of drug alerts comprise basic drug alerts, advanced alerts and complex alert systems (representing a set of CDSSs containing features of both basic and advanced alerts). Two papers in their study investigated the effects of four types of basic alerts, of which three reported statistically significant beneficial effects on prescribing. *Drug allergy warnings* decreased allergy error events by 56% (P=0.009).⁵⁷ It also found that providing default dosing via *basic medication order guidance alerts* resulted in reduced dose errors in two studies of 23% (P=0.02)⁵⁷ and 71% (P=0.0013).¹⁰³ Regarding medication errors, the 40% reduction in error events achieved by *drug-drug interaction warnings* did not reach statistical significance (P=0.89).⁵⁷ The SR study confirms that advanced alert types tend to provide positive effects across the five categories, saying that all the 20 papers evaluated more advanced alert types and statistically significant effects were shown in 21 out of 23 types across five categories.

Shiffman et al. looked at the impact of CDSS on practitioner performance, patient outcomes and satisfaction, with the focus on functionality and the effectiveness of the systems.⁴⁹ The authors studied 25 RCTs, CT and TS which were published between 1992 and 1998. The SR study was conducted using a technological taxonomy, dividing studies between stand-alone and integrated systems and between basic and advanced DSS.

All of the systems displayed relevant patient data, a menu of drugs and a choice of doses. Half of the studies used a system with advanced CDSS functionality while the other used systems with no or limited/basic CDSS. Also, in 14 studies with advanced decision support, the risk reduction was greater than in 11 studies without

advanced decision support, but studies without advanced support were mostly compared to computer-based ordering whereas those with advanced support were compared to manual procedures.

Stand-alone versus integrated systems

None of the 30 SRs included in this analysis directly address differences between “stand-alone” and more “integrated” systems. However, some of the papers do indirectly address this issue offering some insights. We discuss below the salient findings from these studies.

A study of ADEs found that having ADE detection and reporting capability in EHR can improve detection of, and potentially reduce ADE because the EHR system data can be used to identify patients experiencing ADEs.¹⁰⁴ A RCT to explore the impact of an EHR with integrated ePrescribing found positive effects on resource utilisation, provider productivity, and care efficiency.^{48 97}

Eslami et al.³⁴ looked at the characteristics of CDSS for tight glycemic control (TGC) and the effects on the quality of the TGC process in critically ill patient by categorising CDSS into the three features: 1) level of support (merely displaying the protocol chart or suggesting the specific amount of insulin to be administered); 2) the consultation mode (passive or active); and 3) the communication style (in the critiquing mode or in the non-critiquing mode). Most of the CDSS (14 out of 17) were stand-alone and only two papers studied more integrated system.^{105 106} One of these studies¹⁰⁵ reported a reduction in the number of hypoglycaemia events, but without assessing statistical significance.

Interest in the effectiveness of ePrescribing systems continues.¹⁰⁷ The number of systematic review papers on e-Prescribing/CPOE has thus been growing. However, recent reviews have been inconclusive and shown wide variations in findings. For example, Wier et al., who conducted a systematic review of the scientific quality of empirical research on CPOE application, found that there are areas requiring improvement in research designs and analyses.¹⁰⁸ There is a tendency for empirical studies of CPOE to lack adequate study designs and blinding, although there are several high-quality CPOE studies available:

“Current concerns center in the prominent use of pre-post study designs less rigorous measurement techniques, failure to include key information about CPOE and informatics variables, failure to use blinding and inappropriate statistical analyses. These concerns must be addressed to allow the field to build a solid foundation of study generalisability for this area of inquiry in the future.”¹⁰⁸

More importantly, implementation strategies significantly varied and this can lead to confounded results. Apart from the issues of internal validity (e.g. design type, testing of group differences, instrumentation bias and blinding), construct validity including types of ordering functions, level of decision support available, electronic links to other departments, and whether usage is mandated, or measured, implementation strategies used and length of time from implementation to measurement of outcomes and statistical validity are important, but Wier et al. point out how often authors provided little information about the application, technical infrastructure, implementation process or other descriptive data.¹⁰⁸ Such missing information leads to difficulties of generalisability of evidence from studies. Bearing these issues in mind, this section demonstrates key evidence of benefits and risks of ePrescribing, which are relevant to healthcare quality, patient safety and organisational issues, obtained from the relevant literature.

10.5 Implications for policy, practice and research

10.5.1 System integration

Reviewing this body of work has revealed that ePrescribing systems have heterogeneous origins, scope and functionality and are furthermore implemented into diverse organisational settings, all of which may, along with the context of and approach to implementation, influence the risks and benefits that result. As the functionality of these systems extend, these are more appropriately seen as expert systems rather than data processing tools, so the integration or “fit” with organisational knowledge is increasingly seen as important (see Chapter 17). The integration of ePrescribing systems with EHRs is a technical bridge to allow patient-specific information to be used in the delivery of patient-centred care and to minimise the risks of MEs and ADEs as well as improving prescription efficiency.

10.5.2 Knowledge database sharing

In parallel to the integration into EHRs, the integration of CPOE with CDSS is a logical development, which should be encouraged. The rule bases for decision support content can either be locally developed or created centrally, with clear implications for clinician autonomy. However, the open sharing and consolidation of complex rules on drug and diagnosis interactions across healthcare communities offers the possibility of further benefits and efficiencies of scale from ePrescribing that may not have been identified in the more focused studies.¹⁰⁹

Clinicians currently benefit from the development of guidelines on specific conditions, such as the British Thoracic Society's asthma guidelines^{110 111} which can be embedded within CPOE. Guidelines gain legitimacy through the reputation of their sponsoring body, including the National Institute for Health and Clinical Excellence (NICE) and the UK's National Service Framework (NSF).¹¹¹ Implemented CPOE systems need to be able to be updated to keep their knowledge bases up-to-date with this evolving body of knowledge and ideally be able to provide information on the rules being applied to ensure clinician compliance. Aronson emphasises that it is not guidelines alone that influence prescribing behaviour, but also the education and financial incentives to ensure guideline compliance.¹¹¹

10.5.3 System standards

Interoperability with other healthcare information technology systems is a key factor for successful implementation of ePrescribing systems, as the systems are ideally drawing on patient data, updating patient records and integrating with consumable inventory systems. In practice, interoperability is achieved through standards, whether de facto local specifications, proprietary standards of system vendors or conformance with nationally agreed standards. At the heart of standardisation in ePrescribing, as in most areas of health informatics, is the EHR, as there is no point in building decision functionality into a CPOE system that depends upon patient data that are not accessible. As the market for advanced ePrescribing systems develops, the functionality offered by vendors will be shaped by the data on standardised EHRs, pushing vendors to offer functionally similar systems. There is therefore a

need to ensure that EHR standards are extensible to include future patient data needs to prevent functional lock-in for ePrescribing systems.

10.5.4 Implementation of ePrescribing systems from human factors

CDSS interventions may include alerting and reminder systems. Employing advanced guidelines is not in itself sufficient to make sure prompts are acted on, as alerts may be overridden or ignored.¹¹² Consideration of human factors becomes crucial on this point (see Chapter 16). Human factors can be categorised into the following four categories: 1) physical and perceptual factors; 2) cognitive factors; 3) motivational factors; and 4) situational factors. The reasons repeatedly found for overriding alerts included: alert fatigue, disagreement; poor presentation; lack of time; knowledge gap.^{113 114} Procter et al. have argued that human factor considerations are the key to the achievement of effective and safe implementation of healthcare systems and that healthcare professionals' involvement is crucial in system design and development.¹¹⁴

A “user-centred perspective can inform system design to ensure that individual technologies achieve their intended purpose and benefits”¹¹⁵ known as the human-tech approach.¹¹⁶ In order to achieve robust patient safety, the micro (user interfaces, ergonomics) the meso (inter-system communication and integration) and the macro (organisational design) perspectives all need to be addressed during system design.¹¹⁵ Taking these factors into account can increase clinician trust and lead to greater system acceptance. By recognising that ePrescribing systems are fundamentally socio-technical systems and investing in addressing the human factors during design and implementation there will be longer-term gains in lower lifecycle staffing and training costs, reduced risk of errors and greater rule compliance.¹¹⁷

10.5.5 Database for CDSS and data standardisation

As discussed above, to gain the greatest operational gains from ePrescribing requires the systems to draw on knowledge bases of complex rules which can be applied to specific patients. To develop parochial rule bases or rule bases developed

by each system vendor is potentially inefficient. Part of the rule base, for example drug interactions, will be locality-independent, and could be developed globally. Other aspects, such as rules on recommended treatments, may be institution specific and would then need local development and ownership. There is therefore a need for processes to maintain the rule-base, carry out assessments of evidence and provide rule legitimacy. Similarly, there is a policy need for the specification of EHRs to take account of the needs of current and future ePrescribing systems, which will require coordination with the emergent rule-base.

10.5.6 Temporal issues regarding the evaluation of ePrescribing implementation

This overview of the evidence provides very useful insights into the implementation of ePrescribing systems in a variety of contexts and settings. However, systematic reviews can also obfuscate in some respects. This is seen most clearly in the difficulty of addressing the dynamics of the emergence of a new technology. Almost without exception the reviews are atemporal, giving all papers within the review period equal weight. However, Mollon et al. noted that all of the studies they identified showing positive impacts on patients were from after 2005.¹⁵ This suggests, unsurprisingly, that there may have been a change in the technology through time. It can tentatively be proposed that there is evidence in the reviews that this is due to the benefits increasing as the systems take on more advanced decision support functions and become more integrated with other record systems. However, it may also partly be that as experience of these systems increases there is an underlying process of social learning about how these systems can be implemented and used effectively.

Similarly, the studies generally ignore the short-term dynamics of system implementation, taking the implicit assumption that the changes observed shortly after implementation represent the steady-state system performance. In the summarising of most cases it is unclear how the time period of system observation related to the period of implementation, but the pressure to carry out a controlled before-and-after assessment implies that the evidence in most studies is from a period shortly following implementation. The potential danger of drawing conclusions about the long-term impacts based on these snap-shot evaluations is clearest in

comparing the coverage in the reviews of Ammenwerth et al.²⁷ and van Rosse et al.⁵² of the studies in Han et al.⁸² and Del Beccarro et al.⁸³ which studied the same ePrescribing implementation. It is reported that where Han et al. in a shorter study found an increase in mortality, Del Becarro et al. in their longer study did not find the same effect.⁸³ One interpretation of this is that the mortality increase may have been a transient artefact of the organisational change process and that organisational learning and adaptation removed the effect. This is an important insight as it questions the interpretation of the effects identified as significant in many of the papers covered by the systematic reviews in this synthesis.

10.5.7 Synthesised research methods for the studies of eHealth

It is important to address the limitations of a “systematic review” approach for the presentation of solid evidence. While the systematic reviews considered provide valuable insights into the impacts of ePrescribing systems, there is danger that the importance of factors influencing the impacts of ePrescribing systems will be underestimated. There is a trend in the area of health care study that synthesises qualitative and quantitative health evidence.^{118 119} Greenhalgh’s paper on meta-narrative approach towards systematic literature review, *‘Tensions and paradoxes in electronic patient record research: a systematic literature review using the meta-narrative method’* questions the meaning of ‘rigorous’ research engaging with philosophical debates.¹²⁰ Lilford’s paper, *‘Evaluating eHealth: How to make evaluation more methodologically robust’* argues that a mixed research methods approach to evaluating IT systems in health care is needed, questioning the validity of evidence obtained by combining formative assessments with summative ones.¹²¹ The central distinction here is between treating the ePrescribing system as a work-in-progress where it is being recursively shaped by the studies or whether it is treated as a stable “black-box” with the focus of the study being to assess its impacts.

Possible areas which are relatively neglected by the use of “systematic review” and “critical appraisal” methods are:

- Communication amongst different groups of practitioners (e.g. clinicians-pharmacists; clinicians-nurses; pharmacists-nurses, patients- pharmacists, or multi-groups of people of the above)

- Capture of complex changes in work-organisation /workflows
- The impact of institutional differences between national healthcare systems on the shaping of ePrescribing systems and on the outcomes of ePrescribing trials.

Systematic review tries to treat eHealth technologies as scientific objects not as social artefacts which are complex and organic in nature and can potentially lead to unexpected outcomes (see “blackboxing” arguments in the studies of science and technologies¹²²). The systematic reviews examined implicitly assume that the results of small-scale trials can be scaled up, despite evidence that scaling IT systems leads to increasing problems of accommodating wider practice diversity and less identification of users with the systems. The use of short-term studies of recent implementations may overlook the impacts, both positive and negative, on longer term organisational learning. Finally, while the aggregation of short-term studies provides evidence on the impact of the systems on operational risks, it is harder to assess their impact on the risks of rare, but major systemic failure.

10.5.8 Areas for further research

For future research, more sufficiently powered RCTs are needed.^{18 33 51} Such trials are however difficult to mount in this field, and the alternative of time-series based designs, preferably with contemporaneous control groups, should also therefore be considered.¹⁰⁸

Furthermore, research on functionality specific effects or technical specification effects^{33 35 36 48} are urgently needed, in particular evaluating the implementation of commercial systems.^{48 53} In order to make the evidence drawn from such studies, standardised reporting for healthcare IT evaluations is essential.^{27 34 35 42 48} The evaluation of the risk of MEs and ADEs will also be more reliable with the use of standardised metrics and reporting.^{46 47 52 53}

Studying healthcare technology is a complicated task and the evaluation of ePrescribing systems is not an exception. In order to capture a more holistic picture, multi-disciplinary methods are indispensable.^{27 35 36 44} There are a number of studies

adopting before-after and time-series designs, but more evaluation of long-term effects is required. Also, evaluations immediately after implementation need to pay more attention to organisational learning processes with the focus on learning curve.⁵² This allows healthcare professionals to foresee the generalisability of the obtained evidence in their particular organisational settings. Evaluations in long-term care setting will also be useful to assess the long-term impacts.⁵³

In employing a more multi-disciplinary approach to the evaluation of ePrescribing systems, the study of how human factors and socio-technical issues influence the degree of implementation success becomes central.^{35 36 41 45 46} Also, the analysis of macro effects on collaborative work-flow and organisational efficiency is important.⁴⁴
⁴⁵ Finally, comprehensive economic evaluation of immediate and long-term effects is also urgently needed.³⁹⁻⁴²

References

1. Bates DW, Leape LL, Petrycki S. Incidence and preventability of adverse drug events in hospitalized adults. *Journal of General Internal Medicine* 1993;8(6):289-94.
2. Lesar TS, Briceland LL, Delcours K, Parmalee JC, Mastagornic V, Pohl H. Medication prescribing errors in a teaching hospital. *Jama-Journal of the American Medical Association* 1990;263(17):2329-34.
3. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, et al. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. *British Medical Journal* 2004;329(7456):15-19.
4. Davies EC, Green CF, Taylor S, Williamson PR, Mottram DR, Pirmohamed M. Adverse Drug Reactions in Hospital In-Patients: A Prospective Analysis of 3695 Patient-Episodes. *Plos One* 2009;4(2).
5. Howard RL, Avery AJ, Slavenburg S, Royal S, Pipe G, Lucassen P, et al. Which drugs cause preventable admissions to hospital? A systematic review. *British Journal of Clinical Pharmacology* 2007;63(2).
6. Cresswell KM, Fernando B, McKinstry B, Sheikh A. Adverse drug events in the elderly. *British Medical Bulletin* 2007;83(1):259-74.
7. Dobrev A, Stroetmann, K.A., Stroetmann, V.N., Artmann, J.N., Jones, T., and Hammerschmidt, R. The conceptual framework of interoperable electronic health record and ePrescribing systems, 2008.
8. NHS CfH. Patient safety through e-prescribing: E-Health Insider and British Computer Society Health Informatics Forum, 2008.
9. eHealth I. Electronic Prescribing: Toward Maximum Value and Rapid Adoption: Recommendations for Optimal Design and Implementation to Improve Care, Increase Efficiency and Reduce Costs in Ambulatory Care: Washington, D.C., 2004.
10. eHealth I. Electronic Prescribing: Towards Maximum Value and Rapid Adoption., 2004.
11. Kuperman GJ, Reichley RM, Bailey TC. Using commercial knowledge bases for clinical decision support: Opportunities, hurdles, and recommendations. *Journal of the American Medical Informatics Association* 2006;13(4):369-71.

12. Avery AJ, Sheikh A, Hurwitz B, Smeaton L, Chen YF, Howard R, et al. Safer medicines management in primary care. *British Journal of General Practice* 2002;52:S17-S22.
13. Bell DS, Cretin S, Marken RS, Landman AB. A conceptual framework for evaluating outpatient electronic prescribing systems based on their functional capabilities. *Journal of the American Medical Informatics Association* 2004;11(1):60-70.
14. Cornford T ea. Electronic Prescribing in Hospitals: Challenges and Lessons Learning, 2009:71.
15. Mollon B, Chong JJR, Holbrook AM, Sung M, Thabane L, Foster G. Features predicting the success of computerized decision support for prescribing: a systematic review of randomized controlled trials. *Bmc Medical Informatics and Decision Making* 2009;9.
16. Dobrev A, Jones, T., Stroetmann, V., Stroetmann, K., Vatter, Y., Peng, K. Interoperable eHealth is Worth it: Securing Benefits from Electronic Health Records and ePrescribing, 2010.
17. Pollock N, Williams R, D'Adderio L. Global software and its provenance: Generification work in the production of organizational software packages. *Social Studies of Science* 2007;37(2):254-80.
18. Rothschild J. Computerized physician order entry in the critical care and general inpatient setting: A narrative review. *Journal of Critical Care* 2004;19(4):271-78.
19. McDonald CJ, Overhage JM, Mamlin BW, Dexter PD, Tierney WM. Physicians, information technology, and health care systems: A journey, not a destination. *Journal of the American Medical Informatics Association* 2004;11(2):121-24.
20. Bates DW, Cullen DJ, Laird N, Petersen LA, Small SD, Servi D, et al. Incidence of adverse drug events and potential adverse drug events - implications for prevention. *Jama-Journal of the American Medical Association* 1995;274(1):29-34.
21. NHS CfH. ePrescribing: overview and benefits.
22. NHS NPSA. IT requirement Specification Safety Alert: Oral Methotrexate 2.5mg and 10mg Tablets. 2006.
23. Bates DW, Evans RS, Murff H, Stetson PD, Pizziferri L, Hripcsak G. Detecting adverse events using information technology. *Journal of the American Medical Informatics Association* 2003;10(2):115-28.
24. Wolinsky H. Resolution due in medical software regulation. *Annals of Internal Medicine* 1997;127(10):953-54.
25. Caudill-Slosberg M, Weeks WB. Case study: Identifying potential problems at the human/technical interface in complex clinical systems. *American Journal of Medical Quality* 2005;20(6):353-57.
26. Campbell EM, Sittig DF, Ash JS, Guappone KP, Dykstra RH. Types of unintended consequences related to computerized provider order entry. *Journal of the American Medical Informatics Association* 2006;13(5):547-56.
27. Ammenwerth E, Schnell-Inderst P, Machan C, Siebert U. The effect of electronic prescribing on medication errors and adverse drug events: A systematic review. *Journal of the American Medical Informatics Association* 2008;15(5):585-600.
28. Ammenwerth E, Schnell-Inderst P, Siebert U. Vision and challenges of Evidence-Based Health Informatics: A case study of a CPOE meta-analysis. *International Journal of Medical Informatics* 2010;79(4):E83-E88.
29. Bassi J, Lau F, Bardal S. Use of Information Technology in Medication Reconciliation: A Scoping Review. *Annals of Pharmacotherapy* 2010;44(5):885-97.
30. Chatellier G, Colombet I, Degoulet P. An overview of the effect of computer-assisted management of anticoagulant therapy on the quality of anticoagulation. *International Journal of Medical Informatics* 1998;49(3):311-20.
31. Chaudhry B, Wang J, Wu SY, Maglione M, Mojica W, Roth E, et al. Systematic review: Impact of health information technology on quality, efficiency, and costs of medical care. *Annals of Internal Medicine* 2006;144(10):742-52.
32. Clamp S, Keen J. The Value of Electronic Health Records: A Literature Review, 2005.

33. Durieux P, Trinquart L, Colombet I, Nies J, Walton R, Rajeswaran A, et al. Computerized advice on drug dosage to improve prescribing practice. *Cochrane Database Syst Rev* 2008(3):CD002894.
34. Eslami S, Abu-Hanna A, de Jonge E, de Keizer NF. Tight glycemic control and computerized decision-support systems: a systematic review. *Intensive Care Medicine* 2009;35(9):1505-17.
35. Eslami S, Abu-Hanna A, De Keizer NF. Evaluation of outpatient computerized physician medication order entry systems: A systematic review. *Journal of the American Medical Informatics Association* 2007;14(4):400-06.
36. Eslami S, de Keizer NF, Abu-Hanna A. The impact of computerized physician medication order entry in hospitalized patients - A systematic review. *International Journal of Medical Informatics* 2008;77(6):365-76.
37. Fitzmaurice DA, Hobbs FDR, Delaney BC, Wilson S, McManus R. Review of computerized decision support systems for oral anticoagulation management. *British Journal of Haematology* 1998;102(4):907-09.
38. Garg AX, Adhikari NKJ, McDonald H, Rosas-Arellano MP, Devereaux PJ, Beyene J, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes - A systematic review. *Jama-Journal of the American Medical Association* 2005;293(10):1223-38.
39. Georgiou A, Williamson M, Westbrook JI, Ray S. The impact of computerised physician order entry systems on pathology services: A systematic review. *International Journal of Medical Informatics* 2007;76(7):514-29.
40. Hayward GL, Parnes AJ, Simon SR. Using health information technology to improve drug monitoring: a systematic review. *Pharmacoepidemiology and Drug Safety* 2009;18(12):1232-37.
41. Hider P. Electronic prescribing: A critical appraisal of the literature, 2002.
42. Jamal A, McKenzie K, Clark M. The impact of health information technology on the quality of medical and health care: a systematic review. *Health Information Management Journal* 2009;38(3):26-37.
43. Khajouei R, Jaspers MWM. The impact of CPOE medication systems' design aspects on usability, workflow and medication orders: a systematic review. *Methods Inf Med* 2010;49(1):3-19.
44. Niazkhani Z, Pirnejad H, Berg M, Aarts J. The impact of computerized provider order entry systems on inpatient clinical workflow: a literature review. *J Am Med Inform Assoc* 2009;16(4):539-49.
45. Poissant L, Pereira J, Tamblyn R, Kawasumi Y. The impact of electronic health records on time efficiency of physicians and nurses: A systematic review. *Journal of the American Medical Informatics Association* 2005;12(5):505-16.
46. Schedlbauer A, Prasad V, Mulvaney C, Phansalkar S, Stanton W, Bates DW, et al. What evidence supports the use of computerized alerts and prompts to improve clinicians' prescribing behavior? *J Am Med Inform Assoc* 2009;16(4):531-8.
47. Shamliyan TA, Duval S, Du J, Kane RL. Just what the doctor ordered. Review of the evidence of the impact of computerized physician order entry system on medication errors. *Health Services Research* 2008;43(1):32-53.
48. Shekelle PG, Morton SC, Keeler EB. Costs and benefits of health information technology. *Evid Rep Technol Assess (Full Rep)* 2006(132):1-71.
49. Shiffman RN, Liaw Y, Brandt CA, Corb GJ. Computer-based guideline implementation systems: A systematic review of functionality and effectiveness. *Journal of the American Medical Informatics Association* 1999;6(2):104-14.
50. Sintchenko V, Magrabi F, Tipper S. Are we measuring the right end-points? Variables that affect the impact of computerised decision support on patient outcomes: A systematic review. *Medical Informatics and the Internet in Medicine* 2007;32:225-40.
51. Tan K, Dear PRF, Newell SJ. Clinical decision support systems for neonatal care. *Cochrane Database Syst Rev* 2005(2):CD004211.

52. van Rosse F, Maat B, Rademaker CMA, van Vught AJ, Egberts ACG, Bollen CW. The Effect of Computerized Physician Order Entry on Medication Prescription Errors and Clinical Outcome in Pediatric and Intensive Care: A Systematic Review. *Pediatrics* 2009;123(4):1184-90.
53. Wolfstadt JI, Gurwitz JH, Field TS, Lee M, Kalkar S, Wu W, et al. The effect of computerized physician order entry with clinical decision support on the rates of adverse drug events: A systematic review. *Journal of General Internal Medicine* 2008;23(4):451-58.
54. Yourman L, Concato J, Agostini JV. Use of computer decision support interventions to improve medication prescribing in older adults: A systematic review. *American Journal of Geriatric Pharmacotherapy* 2008;6(2):119-29.
55. Classen DC, Metzger J. Improving medication safety: the measurement conundrum and where to start. *International Journal for Quality in Health Care* 2003;15:141-147.
56. Nebeker JR, Hurdle JF, Hoffman JM, Roth B, Weir CR, Samore MH. Developing a taxonomy for research in adverse drug events: Potholes and signposts. *Journal of the American Medical Informatics Association* 2002;9(6):S80-S85.
57. Bates DW, Leape LL, Cullen DJ, Laird N, Petersen LA, Teich JM, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *Jama-Journal of the American Medical Association* 1998;280(15):1311-16.
58. Potts AL, Barr FE, Gregory DF, Wright L, Patel NR. Computerized physician order entry and medication errors in a pediatric critical care unit. *Pediatrics* 2004;113(1):59-63.
59. Bates DW, Teich JM, Lee J, Seger D, Kuperman GJ, Ma'Luf N, et al. The impact of computerized physician order entry on medication error prevention. *Journal of the American Medical Informatics Association* 1999;6(4):313-21.
60. Evans RS, Pestotnik SL, Classen DC, Clemmer TP, Weaver LK, Orme JF, et al. A computer-assisted management program for antibiotics and other antiinfective agents. *New England Journal of Medicine* 1998;338(4):232-38.
61. Mullett CJ, Evans RS, Christenson JC, Dean JM. Development and impact of a computerized pediatric antiinfective decision support program. *Pediatrics* 2001;108(4):art. no.-e75.
62. Shulman R, Singer M, Goldstone J, Bellingan G. Medication errors: a prospective cohort study of hand-written and computerised physician order entry in the intensive care unit. *Critical Care* 2005;9(5):R516-R21.
63. Nies J, Colombet I, Degoulet P, Durieux P. Determinants of success for computerized clinical decision support systems integrated in CPOE systems: a systematic review. *AMIA Annu Symp Proc* 2006:594-8.
64. Balaguer Santamaria JA, Fernandez Ballart JD, Escribano Subias J. Usefulness of a software package to reduce medication errors in neonatal care. *An Esp Pediatr* 2001;55(6):541-5.
65. Commission TA. A Spoonful of Sugar: Medicines Management in NHS Hospitals, 2001.
66. Abu-Zayed L, Farrar K, Mottram DR. Time spent on drug supply activities in United Kingdom hospitals. *American Journal of Health-System Pharmacy* 2000;57(21):2006-07.
67. Murray MD, Loos B, Tu WZ, Eckert GJ, Zhou XH, Tierney WM. Effects of computer-based prescribing on pharmacist work patterns. *Journal of the American Medical Informatics Association* 1998;5(6):546-53.
68. Ross SM, Papshev D, Murphy EL, Sternberg DJ, Taylor J, Barg R. Effects of electronic prescribing on formulary compliance and generic drug utilization in the ambulatory care setting: a retrospective analysis of administrative claims data. *J Manag Care Pharm* 2005;11(5):410-5.
69. Beer J, Dobish R, Chambers C. Physician order entry: a mixed blessing to pharmacy? *J Oncol Pharm Pract* 2002;8:119-26.

70. Wogen SE, Fulop G., Heller, J. Electronic prescribing: improving the efficiency of the prescription process and promoting plan adherence. *Drug Benefit Trends* 2003;15:35-40.
71. Mekhjian HS, Kumar RR, Kuehn L, Bentley TD, Teater P. Immediate benefits realized following implementation of physician order entry at an academic medical center. *Journal of the American Medical Informatics Association* 2002;9(5):529-39.
72. Lehman ML, Brill JH, Skarulis PC, Keller D, Lee C. Physician order entry impact on drug turn-around times. *Journal of the American Medical Informatics Association* 2001:359-63.
73. Bernstein SL, Whitaker D, Winograd J, Brennan JA. An electronic chart prompt to decrease proprietary antibiotic prescription to self-pay patients. *Academic Emergency Medicine* 2005;12(3):225-31.
74. Siegel C, Alexander MJ, Dlugacz YD, Fischer S. Evaluation of a computerized drug review system - impact, attitudes, and interactions. *Computers and Biomedical Research* 1984;17(5):419-35.
75. Walton RT, Gierl C, Yudkin P, Mistry H, Vessey MP, Fox J. Evaluation of computer support for prescribing (CAPSULE) using simulated cases. *British Medical Journal* 1997;315(7111):791-95.
76. Christakis DA, Zimmerman FJ, Wright JA, Garrison MM, Rivara FP, Davis RL. A randomized controlled trial of point-of-care evidence to improve the antibiotic prescribing practices for otitis media in children. *Pediatrics* 2001;107(2):art. no.-e15.
77. Rivkin S. Opportunities and challenges of electronic physician prescribing technology. *Med Interface* 1997;10(8):77-8, 83.
78. Chin HL, Wallace P. Embedding guidelines into direct physician order entry: Simple methods, powerful results. *Journal of the American Medical Informatics Association* 1999:221-25.
79. Overhage JM, Tierney WM, Zhou XH, McDonald CJ. A randomized trial of "corollary orders" to prevent errors of omission. *Journal of the American Medical Informatics Association* 1997;4(5):364-75.
80. Smith BJ, McNeely MDD. The influence of an expert system for test ordering and interpretation on laboratory investigations. *Clinical Chemistry* 1999;45(8):1168-75.
81. Kuperman GJ, Teich JM, Tanasijevic MJ, Ma'Luf N, Rittenberg E, Jha A, et al. Improving response to critical laboratory results with automation: Results of a randomized controlled trial. *Journal of the American Medical Informatics Association* 1999;6(6):512-22.
82. Han YY, Carcillo JA, Venkataraman ST, Clark RSB, Watson RS, Nguyen TC, et al. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system. *Pediatrics* 2005;116(6):1506-12.
83. Del Beccaro MA, Jeffries HE, Eisenberg MA. Computerized provider order entry implementation: No association with increased mortality rates in an intensive care unit. *Pediatrics* 2006;118(1):290-95.
84. Keene A, Ashton L, Shure D, Napoleone D, Katyal C, Bellin E. Mortality before and after initiation of a computerized physician order entry system in a critically ill pediatric population. *Pediatric Critical Care Medicine* 2007;8(3):268-71.
85. Ammenwerth E, Talmon J, Ash JS, Bates DW, Beuscart-Zephir MC, Duhamel A, et al. Impact of CPOE on mortality rates - Contradictory findings, important messages. *Methods of Information in Medicine* 2006;45(6):586-93.
86. Rosenbloom ST, Harrell FE, Lehmann CU, Schneider JH, Spooner SA, Johnson KB. Perceived increase in mortality after process and policy changes implemented with computerized physician order entry. *Pediatrics* 2006;117(4):1452-55.
87. Sittig DF, Ash JS, Zhang JJ, Osheroff JA, Shabot MM. Lessons from "Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system". *Pediatrics* 2006;118(2):797-801.

88. Bradley VM, Steltenkamp CL, Hite KB. Evaluation of reported medication errors before and after implementation of computerized practitioner order entry. *J Healthc Inf Manag* 2006;20(4):46-53.
89. Koppel R, Metlay JP, Cohen A, Abaluck B, Localio AR, Kimmel SE, et al. Role of computerized physician order entry systems in facilitating medication errors. *Jama-Journal of the American Medical Association* 2005;293(10):1197-203.
90. Bates DW. Computerized physician order entry and medication errors: Finding a balance. *Journal of Biomedical Informatics* 2005;38(4):259-61.
91. Morris CJ, Savelyich BSP, Avery AJ, Cantrill JA, Sheikh A. Patient safety features of clinical computer systems: questionnaire survey of GP views. *Quality & Safety in Health Care* 2005;14(3):164-68.
92. Rotman BL, Sullivan AN, McDonald TW, Brown BW, DeSmedt P, Goodnature D, et al. A randomized controlled trial of a computer-based physician workstation in an outpatient setting: Implementation barriers to outcome evaluation. *Journal of the American Medical Informatics Association* 1996;3(5):340-48.
93. Schectman JM, Schorling JB, Nadkarni MM, Voss JD. Determinants of physician use of an ambulatory prescription expert system. *International Journal of Medical Informatics* 2005;74(9):711-17.
94. Tamblin R, Huang A, Kawasumi Y, Bartlett G, Grad R, Jacques A, et al. The development and evaluation of an integrated electronic prescribing and drug management system for primary care. *Journal of the American Medical Informatics Association* 2006;13(2):148-59.
95. Spencer DC, Leininger A, Daniels R, Granko RP, Coeytaux RR. Effect of a computerized prescriber-order-entry system on reported medication errors. *American Journal of Health-System Pharmacy* 2005;62(4):416-19.
96. Overhage JM, Perkins S, Tierney WM, McDonald CJ. Research paper - Controlled trial of direct physician order entry: Effects on physicians time utilization in ambulatory primary care internal medicine practices. *Journal of the American Medical Informatics Association* 2001;8(4):361-71.
97. Tierney WM, Miller ME, Overhage JM, McDonald CJ. Physician inpatient order writing on microcomputer workstations - effects on resource utilization. *Jama-Journal of the American Medical Association* 1993;269(3):379-83.
98. Bates DW, Boyle DL, Teich JM. Impact of computerized physician order entry on physician time. *Proc Annu Symp Comput Appl Med Care* 1994:996.
99. Shu K, Boyle D, Spurr C, Horsky J, Heiman H, O'Connor P, et al. Comparison of time spent writing orders on paper with computerized physician order entry. *Medinfo 2001: Proceedings of the 10th World Congress on Medical Informatics, Pts 1 and 2* 2001;84:1207-11.
100. van der Meijden MJ, Tange H, Troost J, Hasman A. Development and implementation of an EPR: how to encourage the user. *International Journal of Medical Informatics* 2001;64(2-3):173-85.
101. Cordero L, Kuehn L, Kumar RR, Mekhjian HS. Impact of computerized physician order entry on clinical practice in a newborn intensive care unit. *J Perinatol* 2004;24(2):88-93.
102. Fernando B, Savelyich BSP, Avery AJ, Sheikh A, Bainbridge M, Horsfield P, et al. Prescribing safety features of general practice computer systems: evaluation using simulated test cases. *British Medical Journal* 2004;328(7449):1171-72.
103. Teich JM, Merchia PR, Schmiz JL, Kuperman GJ, Spurr CD, Bates DW. Effects of computerized physician order entry on prescribing practices. *Archives of Internal Medicine* 2000;160(18):2741-47.
104. Evans RS, Pestotnik SL, Classen DC, Bass SB, Burke JP. Prevention of adverse drug events through computerized surveillance. *Proc Annu Symp Comput Appl Med Care* 1992:437-41.
105. Dortch MJ, Mowery NT, Ozdas A, Dossett L, Cao H, Collier B, et al. A computerized insulin infusion titration protocol improves glucose control with less hypoglycemia

- compared to a manual titration protocol in a trauma intensive care unit. *Journal of Parenteral and Enteral Nutrition* 2008;32(1):18-27.
106. Boord JB, Sharifi M, Greevy RA, Griffin MR, Lee VK, Webb TA, et al. Computer-based insulin infusion protocol improves glycemia control over manual protocol. *Journal of the American Medical Informatics Association* 2007;14(3):278-87.
 107. Fortescue EB, Kaushal R, Landrigan CP, McKenna KJ, Clapp MD, Federico F, et al. Prioritizing strategies for preventing medication errors and adverse drug events in pediatric inpatients. *Pediatrics* 2003;111(4):722-29.
 108. Weir CR, Staggers N, Phansalkar S. The state of the evidence for computerized provider order entry: A systematic review and analysis of the quality of the literature. *International Journal of Medical Informatics* 2009;78(6):365-74.
 109. Cresswell K, Bates, D.W., Phansalkar, S. and Sheikh, A. KOpportunities and challenges in creating an international centralised knowledge base for clinical decision support systems (CDSS) in prescribing. *Quality and Safety in Health Care* Forthcoming.
 110. British TS. British Guideline on the Management of Asthma: Quick Reference Guide, June 2009.
 111. Aronson JK. A prescription for better prescribing. *British Journal of Clinical Pharmacology* 2006;61(5):487-91.
 112. Strom BL, Schinnar R, Abera F, Bilker W, Hennessy S, Leonard CE, et al. Unintended Effects of a Computerized Physician Order Entry Nearly Hard-Stop Alert to Prevent a Drug Interaction A Randomized Controlled Trial. *Archives of Internal Medicine* 2010;170(17):1578-83.
 113. Van der Sijs H, Aarts J, Vulto A, Berg M. Overriding of drug safety alerts in computerized physician order entry. *Journal of the American Medical Informatics Association* 2006;13(2):138-47.
 114. Procter R, Pappas, Y., Car J., Sheikhh A. and Majeed A. From human factors to human actors: taking user involvement in eHealth systems seriously. Forthcoming.
 115. Cafazzo JA, Trbovich PL, Cassano-Piche A, Chagpar A, Rossos PG, Vicente KJ, et al. Human factors perspectives on a systemic approach to ensuring a safer medication delivery process. *Healthc Q* 2009;12 Spec No Patient:70-4.
 116. Vicente KJ, editor. *The Human Factor*. New York: Routledge, 2004.
 117. Saathoff A. Human factors considerations relevant to CPOE implementations. *J Healthc Inf Manag* 2005;19(3):71-8.
 118. Pearson M. Synthesizing qualitative and quantitative health evidence: A guide to methods. *Sociology of Health & Illness* 2008;30(2):330-31.
 119. Pope C, Mays, Nicholas, Popay, Jennie, editor. *Synthesizing Qualitative and Quantitative Health Evidence: A Guide to Methods*. New York: Open University Press, 2007.
 120. Greenhalgh T, Potts HWW, Wong G, Bark P, Swinglehurst D. Tensions and Paradoxes in Electronic Patient Record Research: A Systematic Literature Review Using the Meta-narrative Method. *Milbank Quarterly* 2009;87(4):729-88.
 121. Lilford RJ, Foster J, Pringle M. Evaluating eHealth: how to make evaluation more methodologically robust. *PLoS Med* 2009;6(11):e1000186.
 122. Williams R, Edge D. The social shaping of technology. *Research Policy* 1996;25(6):865-99.