Knowledge Engineering Complex Decision Support System in Managing Rheumatoid Arthritis

By

Ning Pan

MBBS(China), GradDipCompSc(Australia)

School of Medicine

Faculty of Health Sciences

The University of Adelaide

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TABLE OF CONTENTS

Abstract

Background: The management of rheumatoid arthritis (RA) involves partially recursive attempts to make optimal treatment decisions that balance the risks of the treatment to the patient against the benefits of the treatment, while monitoring the patient closely for clinical response, as inferred from prior and residual disease activity, and unwanted drug effects, including abnormal laboratory findings. To the extent that this process is logical, based on best available evidence and determined by considered opinion, it should be amenable to capture within a Clinical Decision Support Systems (CDSSs). The formalisation of logical transformations and their execution by computer tools at point of patient encounter holds the promise of more efficient and consistent use of treatment rules and more reliable clinical decision making.

Research Setting: The early Rheumatoid Arthritis (eRA) clinic of the Royal Adelaide Hospital (RAH) with approximately 20 RA patient visits per week, and involving 160 patients with a median duration of treatment of more than 4.5 years.

Methods: The study applied a Knowledge Engineering approach to interpret the complexities of RA management, in order to implement a knowledge-based CDSS. The study utilised Knowledge Acquisition processes to elicit and explicitly define the RA management rules underpinning the development of the CDSS; the processes were (1) conducting a comprehensive literature review of RA management, (2) observing clinic consultations and (3) consulting with local clinical experts/leaders. Bayes' Theorem and Bayes Net were used to generate models for assessing contingent probabilities of unwanted events. A questionnaire based on 16 real patient cases was developed to test the concordance agreement between CDSS generated guidance in response to real-life clinical scenarios and decisions of rheumatologists in response to the scenarios.

Results: (1) Complex RA management rules were established which included (a) Rules for Changes in Dose/Agent and (b) Drug Toxicity Monitoring Rules. (2) A computer interpretable dynamic model for implementing the complex clinical guidance

was found to be applicable. (3) A framework for a methotrexate (MTX) toxicity prediction model was developed, thereby allowing missing risk ratios (probabilities) to be identified. (4) Clinical decision-making processes and workflows were described. Finally, (5) a preliminary version of the CDSS which computed Rules for Changes in Dose/Agent and Drug Toxicity Monitoring Rules was implemented and tested. One hundred and twenty-eight decisions collected from the 8 participating rheumatologists established the ability of the CDSS to match decisions of clinicians accustomed to application of Rules for Changes in Dose/Agent; rheumatologists unfamiliar with the rules displayed lower concordance (0.7857 vs. 0.3929, P = 0.0027). Neither group of rheumatologists matched the performance of the CDSS in making decisions based on highly complex Drug Toxicity Monitoring Rules (0.3611 vs. 0.4167, P = 0.7215).

Conclusion: The study has made important contributions to the development of a CDSS suitable for routine use in the eRA clinic setting. Knowledge Acquisition processes were used to elicit domain knowledge, and to refine, validate and articulate eRA management rules, that came to form the knowledge base of the CDSS. The development of computer interpretable guideline models underpinned the CDSS development. The alignment of CDSS guidance in response to clinical scenarios with questionnaire responses of rheumatologists familiar with and accepting of the management rules (and divergence with responses by rheumatologists not familiar with the rules) indicates that the CDSS can be used to guide toward evidence-based considered opinion. The poor correlation between CDSS generated guidance regarding out of range blood results and response of rheumatologists to questions regarding toxicity scenarios, underlines the value of computer aided guidance when decisions involve greater complexity. It also suggests the need for attention to rule development and considered opinion in this area.

Discussion: Effective utilisation of extant knowledge is fundamental to knowledge-based systems in healthcare. CDSSs development for chronic disease management is a complex undertaking which is tractable using Knowledge Engineering and Knowledge Acquisition approaches coupled with modelling into computer interpretable algorithms. Complexities of drug toxicity monitoring were addressed using Bayes' Theorem and

Bayes Net for making probability based decisions under conditions of uncertainty. While for logistic reasons the system could not be developed to full implementation, preliminary analyses support the utility of the approach, both for intensifying treatment on a response contingent basis and also for complex drug toxicity monitoring. CDSSs are inherently suited to iterative refinements based on new knowledge including that arising from analyses of the data they capture during their use. This study has achieved important steps toward implementation and refinement.

Thesis Declarations

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Ning Pan
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Abbreviations

ACR	American College of Rheumatology
ADE	Adverse Drug Event
ADR	Adverse Drug Reaction
ALT	Alanine Transferase
Arava	Leflunomide
AST	Aspartate Transaminase
AZA	Azathioprine
CBE	Complete Blood Examinations
CDSS	Clinical Decision Support System
CPG	Clinical Practice Guideline
CPOE	Computerised Physician Order Entry
CPR	Computer-based Patient Record
Creat Cl	Creatinine Clearance
CRP	C-reactive Protein
DAS	Disease Activity Score
DMARDs	Disease Modifying Anti-Rheumatic Drugs
EBM	Evidence-based Medicine
EMS	Morning Stiffness
ESR	Erythrocyte Sedimentation Rate
eRA	early Rheumatoid Arthritis
eRA-CDSS	early Rheumatoid Arthritis-Clinical Decision Support System
GI	Gastrointestinal
Gold	Intramuscular Myocrisin
GUI	Graphic User Interface
HCQ	Hydroxychloroquine
IM	Intramuscular
LFT	Liver Function Tests
MCV	Mean Corpuscular Volume
MeSH	Medical Subject Headings

mHAQ	modified Health Assessment Questionnaire
MTX	Methotrexate
Neoral	Cyclosporine A
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
RA	Rheumatoid Arthritis
RAH	Royal Adelaide Hospital
RAQoL	Rheumatoid Arthritis Quality of Life Questionnaire
SDLC	Software Development Life Cycle
SF36	36-item Short Form Health Survey
SOA	Service Oriented Architecture
SSA	Sulfasalazine
TNF	Tumour Necrosis Factor
UML	Unified Modelling Language
UNL	Upper Normal Limit
URTI	Upper Respiratory Tract Infection
UTI	Urinary Tract Infection
VAS	Visual Analogue Scale
WHO	World Health Organisation

1 Introduction

Purpose of the Study

Rheumatoid Arthritis (RA) is a chronic autoimmune disease. RA affects primarily the joints and in the absence of effective treatment, causes widespread systemic complications and progressive joint destruction that can lead to disability and/or premature death. Intensive therapy with Disease Modifying Anti-Rheumatic Drugs (DMARDs) has the benefits of reducing symptoms and slowing progression of RA. However, managing RA is a complex task by virtue of the need to consider and prioritise a multiplicity of potential treatments. In addition, DMARDs can be responsible for Adverse Drug Reactions (ADRs). Methotrexate (MTX) is one of the most widely used DMARDs. Adverse effects caused by the administration of drugs such as MTX can be serious or life threatening. Clinicians tailor treatments to accommodate many factors, such as disease activity, the number and location of joints affected, and possible toxic effects associated with drugs, which make decision-making a complicated process intrinsically. Published Clinical Practice guidelines (CPGs) aim to improve clinical decision-making; however, due to factors such as high complexity and a lack of specificity, they have relatively limited immediate impact on clinical practice. Furthermore, implementation research has shown the difficulty rheumatologists' experience in implementing guidelines into clinical practice, and better strategies for translating evidence into rheumatology practice are needed[1].

The early Rheumatoid Arthritis (eRA) Clinic of the Royal Adelaide Hospital (RAH) has been organised to provide prompt assessment and treatment of patients with eRA. The objective is to apply effective treatment in order to achieve remission in RA as soon as is practical, thereby avoiding irreversible joint damage caused by unsuppressed RA. Good decision-making for RA entails a balance between the benefits of treatment and the potential and realised risks of toxic drug effects. The eRA clinic has established the Dose Modification Protocol to assist the clinicians to adjust drug dosages for patients according to the selected disease activity assessment indices and laboratory variables. However, there were considerable exceptions for the clinicians to

fully comply the protocol. I performed a secondary data analysis on the relevant data extracted from the eRA clinical database; the results showed that the clinicians of the eRA clinic integrated additional clinical expertise into their decision-making, which complemented the protocol according to individual patient's particular clinical circumstance. For example, a clinician may breach the protocols because of his or her concern regarding a potential or realised drug toxicity risk or due to other issues including logistical factors and patient preference. Such considerations can also lead to inconsistent protocol compliance by individual clinicians, who may weigh multiple considerations differently at different times.

In order to systematically incorporate up-to-date evidence into clinical decision-making coherently, the eRA clinic aimed to establish a full-scale RA management rules, coexisting with the Dose Modification Protocol. The RA management rules will provide evidence-based recommendations, which aim to assist the clinicians in their decision-making with the intent of achieving a balance between the benefits that accrue from disease suppression and events arising from unwanted drug effects. However in spite of guidance from the use of a paper-based approach, developing a knowledge-based computer application such as CDSS, with the features of delivering complex CPGs will be valuable to assist clinical decision-making. The eRA clinic needs interventions such as CDSSs to facilitate the decision-making process by computerising the complex RA management rules, and to tailoring treatment advice for individual patients according to relevant clinical and laboratory data inputs, thereby supplying best evidence in the most apt way at the time of decision-making. CDSSs also provide the opportunity for violations of the rules to be recorded at the point of care allowing alter evaluation of the reasons for violations and possible improvements in decision-making which can then be incorporated into the CDSS.

In addition, the study conducted a questionnaire to analyse the agreement between the CDSS recommendation and the rheumatologist's decision. This analysis evaluated the guideline compliance. It provided the insights into the acceptance of the guidelines, hence the future practicability of the CDSS. This information is valuable for future refinement of the RA management rules and further improvement of the CDSS.

In summary, the establishment of comprehensive RA management rules and the development of CDSS can facilitate the practice of Evidence-based Medicine (EBM) by utilising up-to-date evidence and case-based data to deliver patient-centred care. When integrated into the eRA clinic workflow, the CDSS can assist clinicians to make consistent, evidence-based decisions in daily clinical practice and thereby achieve better management of RA. This work builds upon the current project to computerise patient data in the eRA clinic that is funded by a grant from the Australian Department of Health and Ageing and administered through the Royal Australasian College of Physicians. The project utilizes patient data from the Rheumatology Unit's ongoing Early Arthritis study (REC Approval No: 981105a). These patients have given written consent for long-term follow-up as part of the study (981105a). This project used the follow-up data during the CDSS development and the questionnaire. The patient data are de-identified and coded, hence the patient data with allocated IDs were used for this project.

Clinical Decision-Making

Clinical decision-making is central to medical practice. Clinical decision-making is a process that clinicians use to determine a patient's needs based on the interpretation of medical observations according to the patient's particular clinical state [2]. Today's ageing population combined with increasingly sophisticated medical technology, make clinical decision-making increasingly complex. This complexity arises from factors such as a high prevalence of chronic diseases, increasing therapeutic options and patients with multiple co-morbidities who are consequently on multiple medications. The growing complexity results in increased uncertainty surrounding many decisions in clinical practice. In response to decision-making under increased uncertainty, clinicians have adopted the practice of EBM. EBM is the conscientious, explicit and judicious use of best evidence sourced from relevant clinical research and clinical expertise in decision-making relevant to the care of individual patients [3]. Submission to the disciplines of EBM is motivated by a desire to make 'good' clinical decisions. A 'good' decision is the identification of an option with the highest expected 'utility' over other alternatives. A '**utility**' is a numerical measurement of preference assigned

to a state or an outcome. According to Bayesian Decision Theory, A decision network represents information about the agent's current state, the agent's possible actions, the state/outcome that will result from the agent's action, and the utility of that state/outcome. When the state or the outcome of the agent's action is unknown, find the utility of each possible state/outcome (action-state pair), and take the action with the maximum expected **utility** [4]. Clinical decision-making reflects how a clinician values a state or an outcome compared with other alternatives regarding to a specific clinical scenario.

Despite the general enthusiasm for adopting EBM in clinical decision-making**,** gaps do exist between optimal practice and actual practice [5, 6]. Barriers such as time constraints for collecting the most recent, relevant medical evidence, and professional inertia in behavioural change required for utilisation of the evidence in daily practice remain. Therefore, a considerable number of clinical decisions are 'suboptimal' because a clinician makes his or her judgment based on outdated evidence or incomplete information or fails to act on new information. There is an increasing interest in facilitating EBM by promoting the implementation of best evidence from research findings to assist optimal decision-making in clinical practice. It is necessary to use efficient and effective practitioner-directed interventions to ensure that changes occur in actual practice. Nevertheless, uncertainty in clinical decision-making remains a problem, which affects the outcomes of decisions that are made based on expected outcomes regardless of the process of decision-making. For any single decision, there is a chance of resulting in a bad outcome. Therefore, evaluating the decision-making process, instead of evaluating a decision by the clinical outcome that follows the decision, will give us the insight into whether an intervention to improve decision-making is better than other competing processes.

People often make errors when confronted with complex problems. Moreover, the combination of time constraints, workload and competing demands in the clinical environment means that errors can occur at any phase in the clinical decision-making process. Clinical errors refer to any mistake made by a healthcare provider in a clinical setting. These errors are often made under a set of conditions within the system in

which individual healthcare providers practice. Making clinical errors during decision-making is a direct cause of poor clinical actions, which can result in unnecessary death or injury. Most clinical errors are preventable through the improvement of decision-making processes before they result in harmful outcomes.

Clinical Decision Support System Aided Decision-Making

Publication of new evidence from clinical research occurs continually. However, new evidence cannot improve the quality of a clinical decision unless healthcare providers incorporate it into their decision-making processes. CPGs are systematically developed, evidence-based recommendations that assist clinicians in decision-making for specific clinical circumstances [7]. Over the past decade, adherence to CPGs has become the gold standard for ensuring quality in clinical practice; however, they have limited impact in clinical decision-making. Extensive evidence in literature and practical experience shows that passive dissemination of CPGs is not sufficient to improve guideline compliance [8-10]. Strategies for incorporating EBM into decision-making processes are needed [6, 11, 12]. Furthermore, there is additional best evidence that can be integrated into decision-making to complement CPGs, because CPGs provide generic recommendations, and are not expected to address all aspects of patient care. Therefore, establishing systematic approaches, which incorporate this additional best evidence into clinical decision-making processes, are also needed.

Information technology has been introduced to assist healthcare practice for more than two decades [13]. Information systems enhance data storage, data retrieval, as well as the manipulation of data. Clinical Decision Support Systems (CDSSs) are information systems specifically designed to aid clinical decision-making [14]. There is clear evidence that CDSSs are able to assist clinicians in practicing EBM, prevent errors and detect adverse events by delivering useful information when needed [15-19]. CDSSs have benefits for healthcare, which is demonstrated through automated checks for unwanted interactions, reminders and alerts, and the delivery of CPGs [20-24]. Studies also show that computer-based CPG implementation systems improve guideline compliance [20, 25, 26]. However, there is consensus that CDSSs are little used in real

clinical settings despite their promising benefits. Numerous obstacles need to be overcome before realising an optimal CDSS. Issues such as adaptation of guidelines for electronic implementation and integration with clinical workflow make implementing CDSSs a challenging task [27]. Furthermore, the extent to which CDSSs will be effective and practical in a real clinical setting remains unclear. More research is needed into the issues regarding clinical effectiveness and acceptance of CDSSs [28]. Figure 1.1 illustrates that practising EBM with the aid of CDSSs plays a role to close the gap between the optimal practice and the actual practice. CDSSs can deliver CPGs' recommendations, therefore reinforce the compliance of CPGs; CDSSs can present additional clinical evidence which has not been included into CPGs, CDSSs can also display relevant clinical information when needed.

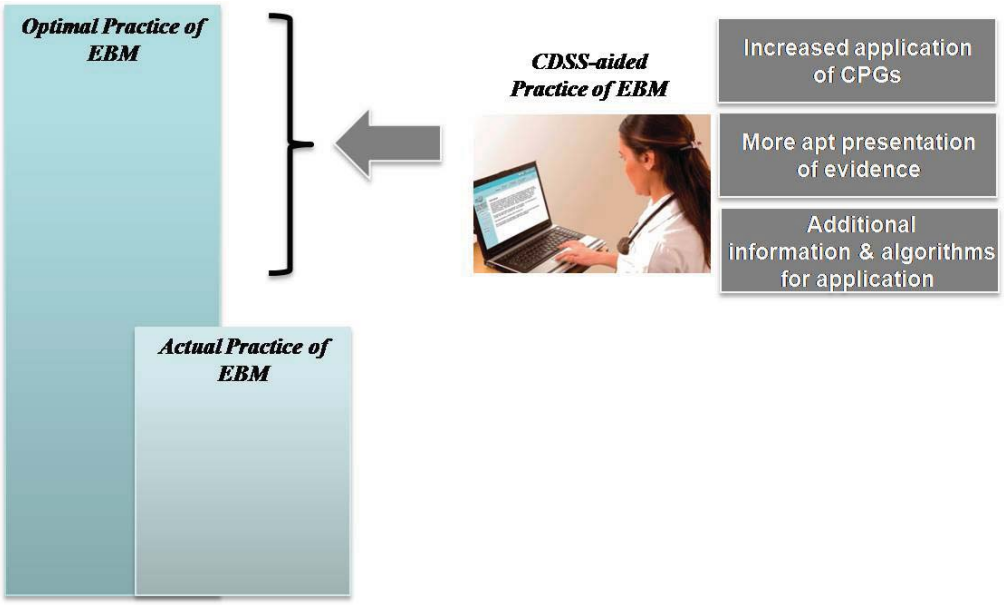


Figure 1.1 Closing the gap with CDSS-aided practice of EBM

2 Literature Review

2.1 Practising Evidence-based Medicine

Over at least the last decade, EBM has been the guiding mantra of clinical practice. EBM integrates clinical expertise with current best evidence from clinical care research to manage the individual patient [3]. Evidence-based clinical practice represents an approach to decision-making, in which the clinician uses the best evidence available, in consultation with the patient, to decide upon the option that suits that patient best [29]. However, to incorporate new evidence and relevant research findings into daily clinical practice remains a challenge for clinicians. Research has revealed the difficulties in persuading health professionals to actually practice EBM in patient care [16].

CPGs have been widely promoted for more than two decades, CPGs are defined as 'systematically developed statements to assist practitioner and patient decisions about appropriate healthcare for specific clinical circumstances' [30]. It is believed that CPGs have the potential to play an important role in narrowing the gap between evidence and practice in daily medical practice. Health professionals have been encouraged to develop and apply guidelines that assist in clinical decision-making in order to achieve better quality healthcare and patient outcomes. Nevertheless, Gaps have been identified between evidence and practice [5, 12, 31], CPGs have had limited impact on clinical practice or health outcomes [8]. A structured review of guidelines from medical literature shows that adherence is not as good as might be expected [9]. Barriers such as a lack of agreement with specific guidelines and a lack of self-efficacy have been identified as affecting clinicians' adherence to guidelines [32, 33]. In addition, conventional narrative CPGs, which give general population-based recommendations, are not specific for the individual patient. Difficulties in accessing CPGs in real time during consultations add to these difficulties in applying them to specific patients [34]. Haynes identified special problems in applying evidence in clinical practice [31]; they are (1) the lack of agreement on evidence standards, which undermines the effectiveness of authoritative practice guidelines, (2) ineffective and

inefficient application of evidence and practice guidelines due to mismatches in evidence and usual practice circumstances, and (3) time constraints, which undermine the interpretation and application of evidence.

Moreover, adhering to clinical guidelines depends on whether physicians are sufficiently influenced by the guidelines to change their behaviour. Farquhar et al. systematically reviewed 153 surveys of clinicians' attitudes to CPGs. They found that clinicians' attitudes to clinical guidelines were positive in most cases [8]. However, for individual clinicians, the barriers to making significant changes to their practices included the need for educational, organisational and structural changes in the healthcare system.

Passive dissemination of information, such as CPGs or educational materials, are generally not effective [6]. Lomas et al. evaluated a series of published guidelines and found that it took an average of approximately five years for routine practice to follow these guidelines [35]. This indicates that the current practice of medicine significantly lags behind the standard of medical knowledge**.** Numerous studies have suggested that using specific and effective strategies to implement research-based best evidence ensures that practices change [6, 11, 12]. Bero et al. systematically reviewed rigorous studies from 1966 to 1995 regarding the effectiveness of different strategies for the dissemination and implementation of research findings. They concluded that computerised decision support systems are among the most effective interventions [6].

2.2 Electronic Health Record and Computer-based Patient Record

Electronic Health Record (EHR) is a lifetime patient record in digital format that includes all information from all specialties and requires full interoperability [36]. The establishment of EHR enables sharing and exchange of patient clinical data between disparate systems. Implementing EHR offers remarkable opportunities for practicing EBM using Clinical Information Systems (CISs) and CDSSs to improve healthcare [15, 16]. However, to implement EHR at a national level or even at an international level faces enormous political and social challenge.

Computer-based Patient Records (CPRs) are increasingly used in today's clinical care, clinical research, and health system management [37]. However, as CPRs are relatively unsophisticated and lack standard nomenclature or vocabularies, the task of implementation is complex [38]. Translating free-text clinical notes into computer-legible codes presents a challenge [39]. Coded data with a structured format can be restrictive when compared to the free text in paper-based charting systems [40]. Regardless, CPRs provide a solid foundation of information to be used during the care process and as a source of scientific data.

There are many clinical benefits of CPRs [41]. First of all, they provide easy access to patients' charts, in that data can be accessed simultaneously from many locations, and can be printed out using a variety of fonts, colours, and sizes that help draw the clinician's attention to the most important data. Parallel access to patient data from different locations enhances clinical workflow and improves work processes. Secondly, CPRs assist clinicians in decision-making as patient data are structured and coded in an unambiguous fashion by software programs or clinical decision support tools that continually check and filter data for errors, summarise and interpret data, and issue alerts and/or reminders for clinicians, as they monitor for unwanted events that may develop into organ-threatening or life-threatening complications. Thirdly, CPRs can be integrated with computerised CPGs to deliver patient-specific recommendations when and where needed. In addition, images can be combined with textual data to create a more complete 'picture' of the patient's condition. The accuracy of data in CPRs is therefore of great importance [37] and should improve as the use of CPRs increases.

2.3 Clinical Decision Support

Clinical decision support is described as an aggregate of electronic information resources that enable practicing clinicians to quickly obtain bottom-line summary information on clinical topics to aid in decision-making at the point of care. CDSSs are software packages designed specifically to aid clinical decision-making. Recommendations tailored to individual patients can be presented to the clinician or

patient for decision-making from a computerised clinical knowledge base. CDSSs are especially important for the practice of EBM as they can close the gap between evidence and practice and thereby improve the quality of healthcare [15, 16].

Published studies show that CDSSs improve clinicians' performance [14, 42, 43]. Hunt et al. systematically reviewed controlled clinical trials of patient care with a CDSS comparing with care without one from 1974 to 1998, and found a beneficial effect on physician performance in 43 of 65 studies (66%). Six out of fourteen studies assessing patient outcomes also found a benefit.

CDSSs can benefit health care by preventing errors and adverse events, by facilitating a more rapid response to adverse events, and by tracking and providing feedback about adverse events [19, 44]. Research shows that a Computerised Physician Order Entry (CPOE) with embedded decision support features substantially decreased medication error rates [18]. A systematic review also showed that the use of CDSSs significantly decreased medication error rates [17].

Specific CDSSs, such as computerised reminders and alert systems, have increasingly demonstrated their effectiveness in modifying clinician behaviour in drug management and preventive care. Shea et al. performed a meta-analysis, which concluded that computer-based reminder systems improved prevention services [23]. Dexter et al. performed a randomised controlled study and found that computerised reminder systems increased the delivery of preventive care to hospitalised patients [22]. Bennett et al. systematically reviewed the benefits of computerised reminders based on 76 randomised controlled trials of computer-generated medication reminders directed at clinicians or patients. Their results showed that computerised reminders can improve various behaviours related to drug management, and patient-directed reminders can improve medication adherence [21]. Raschke et al. developed and evaluated a computerised alert system to correct errors that might lead to Adverse Drug Events (ADEs) [24]. During the evaluation period, the alert system fired 1116 times and 53% of the alerts were true-positive alerts. Of the 596 true-positive alerts, 265 were not identified by the physician prior to alert notification (effective value of 44%). This

study indicates potential for physicians to be prompted to act in a more timely manner and thereby avoid possible patient harm associated with ADEs, and demonstrates that computerised alert systems can detect ADEs in a timely and cost-effective way to prevent patient harm.

However, CDSSs do not always enhance clinical practice. The successful implementation of CDSSs needs carefully designed procedures for the delivery of information. Bennett et al. suggest that the most effective way of presenting information is to deliver it close to the time of decision-making [21]. Patterson et al. claim that human factors, such as arduous workloads, are a barrier in the use of computerised reminder. [45]. Kawamoto et al.'s systematic review identified features critical to success in improving clinical practice using CDSSs; multiple logistic regression analysis shows four independent predictors; they are (1) integrating into clinical workflow, (2) providing clinical recommendations rather than assessments, (3) providing decision support at the time and location of decision-making and (4) using computers to generate the decision support [46].

Nevertheless, CDSSs provide valuable assistance to clinicians by performing complex evaluations based on patient-specific information and presenting the results and recommendations in a timely fashion. In order to be widely accepted by practicing clinicians, CDSSs must be integrated into clinical workflows and be able to provide the right information at the right time without extra effort [16] [47]. More research is needed to reveal the factors pertaining to the successful implementation of CDSSs [17].

2.4 Computerised Clinical Practice Guideline

CPGs are commonly delivered in a paper-based format to guide clinical decision-making. However, clinicians have not incorporated paper-based clinical guidelines into their practices as expected [8, 9, 32, 33]. Recently published research has shown that information technology can provide valuable assistance to health professionals in adhering to CPGs, and consequently reduce harmful practice variations and improve patient outcomes [18, 19, 44]. Yet, simply placing CPGs on a computer network does

not necessarily increase guideline adherence [48]. Stolte et al. suggested that computerised CPGs should be integrated into the clinical decision-making process for better CPGs compliance.

The implementation of computer-based guidelines promises to improve the acceptance of CPGs in the clinician's daily practice. Lobach et al.'s research revealed that a computerised diabetes management protocol significantly improved clinicians' compliance with guideline recommendations [25]. Sintchenko et al. also demonstrated that computer-based decision support with recommendations for prescribing antibiotics significantly improved the quality of decisions [20]. Shiffman et al. performed a systematic review, which concluded that guideline compliance improved in 14 out of 18 computer-based guideline implementation systems [26].

However, obstacles remain regarding guideline adaptation for electronic implementation. Wang et al. reviewed literature on guideline representation models; they found that the representation of CPGs in a computer-interpretable format is a critical issue for guideline development and implementation [49]. Moreover, an understanding of clinical workflow is a critical step in the success of implementing computer-based CPGs [27, 50]. Workflow integration is a strong impediment in the successful implementation of a computer intervention. Eccles et al. [51] performed a trial study, which concluded that integrating systems into clinical environments remains a challenge even though the technical problems of producing such a system are solved.

In conclusion, several issues relating to guideline-based CDSSs, such as guideline representation and workflow integration, need to be addressed more intensively. Substantial work remains to be done to realise the potential benefits of computerised CPGs.

2.5 Review of Managing Rheumatoid Arthritis

2.5.1 Rheumatoid Arthritis

RA is a chronic disease that affects approximately 1% of the adult population worldwide [52]. RA is heterogeneous with natural fluctuations in clinical course. RA primarily affects joints and often causes progressive joint destruction, which leads to progressive disability. Non-articular complications, particularly those involving the cardio-vascular system can lead to premature death. RA develops predominantly in people aged between 20-50 years and once acquired is generally a lifelong affliction that reduces quality of life [53]. While recent advances in treatments have yielded better outcomes, for best results interventions need to be applied early and continuing treatments and continual optimisation of treatments as drug 'resistance" or intolerance develop through the course of the disease, are generally required.

2.5.2 Rheumatoid Arthritis Management Goal

The principal goal of managing RA is to suppress the disease. This entails eliminating symptoms and signs of joint and systemic inflammation as soon as practicable and to thereby minimise joint damage. This approach when applied in a timely manner with sufficient intensity can often achieve remissions and prevent disability [54].

2.5.3 Modern Treatment of Rheumatoid Arthritis

In recent years RA has been treated earlier and more intensively than previously [55-59]. Detecting and treating RA at its earliest stages offers many patients the prospect of RA remission [57]. While non-steroidal, anti-inflammatory drugs (NSAIDs) can be used for symptomatic relief during the period of initial evaluation of RA, they are no longer considered adequate, even for milder RA, as they are associated with significant unwanted effect, have not been shown to favourably influence disease progression in RA and their widespread use may have contributed to the increased risk of cardiovascular events associated with RA [60]. This perspective contrasts with the now obsolete 'pyramidal' approach to the management of RA which restricted use of longer acting DMARDs to patients whose symptoms were not reduced to tolerable

levels by NSAIDs [61] or who had already developed radiographic evidence of joint damage. In contrast to NSAIDs, DMARDs do not have a direct analgesic action but have been shown to reduce symptoms and signs of RA and to inhibit damage caused by synovial inflammatory tissue (pannus) to peri-articular bone (erosions) and to maintain physical function in the longer term [52, 62]. Recent studies indicate that DMARDs should be introduced as soon as a diagnosis of RA can be established and that doses should be adjusted and other DMARDs added in a timely fashion until the patient has achieved a low level of disease activity and preferably remission [63].

Rheumatology professional organizations have updated guidelines to adopt new approaches that have been shown to be superior to the traditional approach to management of RA. For example, the American College of Rheumatology has published updated guidelines for managing RA [52, 64]. The Scottish Intercollegiate Guidelines Network published a national clinical guideline for management of RA [65].

2.5.4 Toxicity of DMARDs Therapy

In DMARDs therapy for RA, inefficacy and adverse drug effects are the two main limiting factors. When drug doses are increased due to lack of efficacy, potential and realised drug toxicity become an increasing concern. Therapy-related, severe drug toxicity can cause irreversible organ damage and lead to life threatening complications. Treatment-related adverse effects are the predominant reason for discontinuing an effective drug; thereby limiting potential benefits of the therapy. Ultimately 30% of RA patients have had experience with discontinuation of one or more drugs for toxicity reasons, irrespective of the drug used [66].

Clinical trials have clearly defined the toxicity profiles of the individual DMARDs [66-69]. However, when drugs are used in combination or in a “real-life” setting, therapy may disclose different toxicity manifestations [70]. Instances of increased toxicity have been reported when combined DMARDs therapy is introduced [71]. Therefore, it is important for clinicians to monitor patients during the treatment of RA over the longer term in order to prevent serious drug toxicity and thereby achieve drug use that is as safe as possible.

2.5.5 Balancing Risks and Benefits

There is no stand alone wholly effective treatment for RA and no treatment that is free from safety concerns. While RA treatments are generally more effective when given in combinations, in practice, concerns regarding the potential for more frequent adverse events have limited the application of this approach. Thus clinicians face an ongoing challenge of making clinical decisions that balance benefits against perceived risks, while taking account of the patient's prior experiences and concerns. There is also a need subsequently to make adjustments in light of responses and tolerance to interventions undertaken [53].

2.5.6 Guidelines in Rheumatoid Arthritis Management

Clinical guidelines and algorithms are essential elements in guiding clinical decision-making [72, 73]. There are numerous guidelines that have been published to manage RA [52, 64, 65, 74], as well as guidelines developed to monitor DMARDs therapy during the management of RA [75-77]. However, these guidelines give general recommendations; they define a range of acceptable practices or a range of management options rather than give specific detailed recommendations. Therefore, they have limited immediate impact on clinical practice.

Research has illustrated the difficulty that rheumatologists have in implementing guidelines into clinical practice, and suggests that additional strategies that incorporate evidence into practice in rheumatology should be studied [1]. Ellrodt et al. [72] introduced the concept of developing and implementing a framework to aid in decision-making for managing patients with chronic musculoskeletal diseases. Cannella et al. [55] suggested rheumatologists should use a treatment algorithm as a guide in the treatment of RA.

Collectively, a better understanding of how to utilise RA management options more effectively [56] and the development of more specific guidelines that deal with narrow clinical scenarios is needed [74].

2.5.7 Computer Aided Approach of Managing Rheumatoid Arthritis

While managing RA is generally regarded as requiring multidisciplinary approach, in eRA prompt, systematic pharmacological interventions appear to yield the greatest impact on long-term outcomes However, in spite of a burgeoning trend toward eRA clinics, there is comparatively little data that compare outcomes achieved by different practices and practitioners [78].

The Swedish Society of Rheumatology introduced a national Swedish surveillance registry for patients with eRA in 1994. It collected data from all the rheumatology units nationally across Sweden. One of the major goals of the project was to construct a structured data registry that could be used in future software developments that would enable physicians to enter data directly, while providing graphical and historical information on the individual patient in the regular out-patient clinic. The registry led to a substantial change in drug prescription patterns in some units, and has played a role in the optimisation of treatment and new therapy evaluations for the future. Using the surveillance registry in the management of RA illustrates that computerised clinical tools can guide and improve daily clinical practice to achieve better patient outcomes.

2.6 Review of Adverse Drug Reactions

Adverse Drug Reactions (ADRs) can cause significant morbidity and mortality. The World Health Organization's (WHO) definition of an ADR is 'a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function'. Most ADRs happen in patients who are prescribed treatment within the limits of accepted clinical practice [79].

ADRs are common in the Australian health system [80]. At least 80,000 medication-related hospitalisations occur each year in Australia, with an estimated cost of $350 million annually [81]. A review of medical records has indicated that up to 69% of these hospital admissions are considered preventable [80, 81].

There is a trend in contemporary healthcare of increasing ADRs. Recently, Burgess et al. completed a study, which analysed ADRs causing or extending hospital admissions in people aged 60 years or over in Western Australia. The figures showed that hospitalisations associated with ADRs in people of this age more than doubled between 1991 and 2002 [79], and had increased almost fivefold in between 1981 and 2002, with the figures continuing to rise until the end of the study. The study also pointed out that the most common drugs involved were cytotoxic and anti-rheumatic agents. In 2002, a report from the Australian Council for Safety and Quality in Health Care showed that statistics of hospital related ADRs for South Australia in all age groups increased fourfold between 1988/89 and 2000/01, and correlated strongly with changes in medication use in the community [82].

These data underline the importance of investing in systems for prevention and management of ADRs. Revision of clinical guidelines, identification of populations at risk and improved patient monitoring are recognised methods for addressing the ADR issue [79, 80, 83]. While interaction checking is a well established application of decision support technology used by prescribers, clinical trials are needed to explore the potential benefits of more complex CDSSs in patient care.

2.7 Review of Methotrexate in Rheumatoid Arthritis

2.7.1 Methotrexate Combination Therapy

Methotrexate (MTX) is the most widely used DMARD for the treatment of RA. Multiple randomised controlled trials have established the efficacy and tolerability of MTX [84-88].

During the past decade, treating RA patients with more intensive therapies that combine MTX with other DMARDs have shown superior clinical responses and patient benefits [53, 62, 89]. MTX, when used in combination with cyclosporine A, has been shown to improve disease control without a significant increase in toxicity [90, 91]. MTX plus hydroxychloroquine is one of the most effective and best tolerated

DMARD combinations [92, 93]. The combination of MTX and sulphasalazine also has a positive clinical effect [94-96]. Lehman et al. performed a randomised, double-blind controlled trial, which showed that the addition of weekly intramuscular (IM) myocrisin (Gold) caused significant clinical improvement in RA patients with a suboptimal response to MTX [97]. No clear advantage was seen with the addition of azathioprine to MTX [98-100].

More recently, a randomised, double-blind, placebo-controlled trial showed that addition of leflunomide yielded clinical benefit in RA patients taking MTX and was well tolerated [101]. The combination of sulfasalazine-hydroxychloroquine-methotrexate, also known as 'triple therapy', is being used increasingly in RA [62] as multiple studies have shown that it is a very effective therapy and well tolerated in the majority of patients [102-105]. Collectively, it has become apparent that MTX combination therapies offer substantial clinical improvements in comparison to single drug therapies. The advantages of use with MTX extend to the newer biological agent therapies, such as tumour necrosis factor (TNF) blockers [106].

2.7.2 Drug Action Analysis for Methotrexate Toxicity

Drug toxicity may occur through the over dosage of medication, an accumulation of the drug in the body over time, or the inability of a patient's body to eliminate the drug. MTX is a potent folate antagonist that inhibits dihydrofolate reductase, which is an enzyme necessary for the formation of tetrahydrofolate, which is needed for thymidylate biosynthesis and purine biosynthesis. MTX inhibits DNA formation and thereby reduces cell replication. MTX is used to treat a wide variety of cancers, psoriasis and RA. These conditions all have in common abnormal rates of cell replication.

In RA, MTX is used in doses substantially lower than those used in cancer chemotherapy. It is thought to act, at least in part, by suppressing replication of leucocytes and other immune cells that are needed to sustain the intensity of the unwanted inflammation that is the hallmark of this condition. Due to the fact that MTX inhibits cell division by inhibiting DNA formation, MTX toxicity occurs mainly

in tissues that are involved in cell renewal, including bone marrow, gastrointestinal tract mucous, skin, etc., although the mechanism of MTX liver toxicity is not very well understood. It has been suggested that hypersensitivity is responsible for most MTX pulmonary toxicity [107, 108]. MTX is primarily excreted by the renal route. In patients with impaired renal function, MTX can accumulate to toxic levels with marrow suppression being a salient issue [109].

2.7.3 Methotrexate Toxic Effects Analysis

As the therapeutic effect of MTX and its most frequent unwanted effects are both dose-related, MTX therapy is commonly limited by intolerance. Most often this takes the form of non-threatening post-dose nausea and upper gastro-intestinal symptoms [110-113]. More serious adverse events can occur, including lung [114, 115], liver [116, 117] and haematological toxicity [118, 119]. Fatal events have been reported.

MTX toxic effects can affect individual people in different ways. Drug toxicity-related symptoms can be useful for predicting more progressive and severe life-threatening toxicity events. It is important when summarising MTX toxicity, to distinguish potential life threatening events from minor side effects [66]. Wilke et al. [109] has provided a classification schema of adverse effects associated with MTX, which makes this distinction. Alarçon et al. [110] advised temporary and permanent discontinuation of MTX in response to minor and major toxicity events respectively. I have outlined MTX common minor side effects and MTX major toxicity in RA (Table 2.1).

Table 2.1 Methotrexate Toxic Effects in RA

Minor side effects	Gastrointestinal: nausea, vomiting, abdominal pain, diarrhoea Haematological: mild/transient myelosuppression Hepatic: mild/transient elevations of hepatic enzymes Skin/Mucocutaneous: rash, stomatitis Neurologic: fatigue, headache, dizziness Others: fatigue, hair loss
Major toxicity	**Bone Marrow Toxicity:** Methotrexate may produce marked depression of bone marrow, such as anaemia, aplastic anaemia, macrocytic anaemia, leukopenia, neutropenia, thrombocytopenia and bleeding. Pancytopenia may occur and is potentially fatal. **Gastrointestinal Toxicity:** Diarrhoea and ulcerative stomatitis are frequent toxic effects; haemorrhage enteritis and death from intestinal perforation may occur. **Hepatotoxicity:** Methotrexate may be hepatotoxic, particularly at high dosage or with prolonged therapy. Liver atrophy, necrosis, cirrhosis, fatty changes and periportal fibrosis have been reported. Acute increases in transaminase and bilirubin concentrations are common with high doses. **Pulmonary Toxicity:** Methotrexate-induced lung disease may occur acutely at any time during therapy. It is not always fully reversible. Reversible eosinophilic pneumonitis occurs most commonly. Pulmonary fibrosis is uncommon but may be fatal. ❖ Impaired renal function can contribute to haematological toxicity and hepatotoxicity.

2.7.4 Literature Review of Risk Factors for Methotrexate

Although the toxicity profile of MTX is well defined, defining risk factors for MTX toxicity in a clinical context is challenging because susceptibility to drug-related toxic effects may vary widely between individuals. MTX toxicity is affected by many factors, including advanced age, drug dosage, concomitant drugs, pre-existing complications and environmental effects [120].

There is a limited literature focusing on identifying risk factors for toxicity prediction in RA [71]. I performed a systematic review of medical literature for the risk factors associated with MTX in RA using the MEDLINE database provided by PubMed. Bibliographies of papers and articles retrieved were cross-checked for further relevant articles. Search terms included the Medical Subject Headings (MeSH) of 'Methotrexate', 'Arthritis, Rheumatoid', 'Drug Toxicity', 'Risk Factors', 'Risk Management', 'Lung/drug effects', 'Liver Function Tests', 'Hepatitis, Chronic', 'Blood Cell Count', 'Neutropenia', 'Pancytopenia' and 'toxicity' [Subheading]. A review of relevant literature showed that risk factors for MTX toxicity can be identified from the patient's medical history, as well as from patient symptoms and laboratory investigations. I have summarised the details of this literature review, such as reference title, study type and identified risk factors, in a separate table (Table of MTX Toxicity Risk Factors), which is listed in the appendices.

Research into candidate genetic polymorphisms for MTX toxicity risk is in its infancy, although preliminary observations hold promise for improved prediction of therapeutic ratios [121].

2.7.4.1 Common Risk Factors for Methotrexate Toxicity

The common known risk factors for MTX toxicity include advanced age [111, 113, 122, 123] and impaired renal function [112, 123, 124], while more recently, a lack of folate supplementation has been shown to be a risk factor in MTX toxicity [125-129].

McKendry et, al. [111] conducted a 13 year, retrospective study of 144 RA patients treated with MTX; they found advanced age was associated with increased discontinuation of treatment due to major toxicity. Buchbinder et, al. [113] analysed data from 587 RA patients treated with MTX therapy in Australia; results showed that higher rates of toxicity were associated with the older age group (>65) than the younger age group (<65). Wolfe et, al. [122] conducted a retrospective review; they found more gastrointestinal complaints and more pulmonary complaints in older age groups. Mielants et, al. [112] suggest that potentially dangerous side effects are more likely to occur in patients with impaired renal function. An analysis performed on data from 11 MTX clinical trials, including a total of 496 RA patients treated with MTX, showed patients with renal impairment had a higher overall rate of toxicity, and also a higher risk of severe pulmonary toxicity [124].

2.7.4.2 Risk Factors for Methotrexate Pulmonary Toxicity

Methotrexate-related pneumonitis is one of the hazardous adverse effects of treatment for RA. Reports of MTX-related pneumonitis with low-dose MTX therapy emerged in the early 1980s [114, 115]. However, relatively little is known about associated risk factors and strategies for risk avoidance are not well developed.

There are numerous studies which identify a history of smoking [130, 131], pre-existing pulmonary disease [107, 130, 132, 133] and abnormalities in chest radiographs [134] as risk factors. In addition, because of the potential for fatal toxicity, recommendations have been made that development of pulmonary symptoms, such as shortness of breath, cough and fever, should be considered signs of possible lung toxicity while patients take MTX during RA treatment and that treatment should be withdrawn [135-137].

Searles et, al. [130] reported four cases and reviewed six published cases in the literature; they concluded that smoking and pre-existing pulmonary disease were risk factors for pulmonary toxicity and that patients developing suggestive clinical symptoms should be monitored closely. Golden et al. performed a case-review study

[132], which found a significant difference in occurrence of MTX pneumonitis during low dose MTX therapy for RA between groups of patients with and those without pre-existing lung disease . Carroll et, al. conducted a case-control study [107], and concluded that hypersensitivity is probably responsible for most cases of pneumonitis associated with MTX, but pre-existing lung disease may confer increased risk. The case-control study by Alarçon et, al. [131] found that MTX-related lung injury in RA is associated with age, smoking, rheumatoid pleuropulmonary involvement, previous use of antirheumatic drugs and low serum albumin.

2.7.4.3 Risk Factors for Methotrexate Hepatic Toxicity

Cirrhosis and fibrosis are the best recognised long-term unwanted hepatic effects of MTX treatment [116], and liver biopsy studies have shown that long-term MTX therapy for RA is associated with changes in liver morphology [138].

Alcohol abuse [139, 140], obesity [126, 139, 141-143], diabetes mellitus [141], MTX dose [139, 140, 144], treatment duration [139], elevated liver enzymes [139, 144], advanced age [139, 144] and hepatitis are the most consistent risk factors for hepatic fibrosis.

In a retrospective study conducted by Shergy et al. [141], 210 liver biopsies were performed on RA patients treated with MTX from 1979 to 1988. The study concluded that the prevalence of MTX hepatotoxicity in patients with RA receiving long-term low dose MTX therapy is low, and diabetes mellitus and obesity might be potential risk factors of hepatic fibrosis.

Kremer et al. [139] performed a prospective cohort study and found that long-term MTX therapy in RA was associated with a statistically significant worsening in hepatic histologic grade; a history of alcohol consumption, obesity, dosage, treatment duration and a total number of aspartate transaminase (AST) elevations were strongly associated with progression of liver histological grade.

Whiting-O'Keefe et al. [140] conducted a meta-analysis of 15 studies (a total of 636 patients) that examined the relationship between long-term MTX therapy and liver fibrosis. They found that a total cumulative dose and a history of alcohol abuse increased the risk of advanced grades of histologic change on liver biopsies in RA patients undergoing long-term, low dose MTX treatment.

Walker and co-workers [139] surveyed rheumatologists to identify cases of serious liver diseases (cirrhosis and liver failure) in patients taking low dose MTX for RA for 5 years or more. They identified 24 cases and estimated that this complication occurred in about 1 in 1,000 cases treated for this duration. In comparisons between cases and case-controls (taking MTX for RA without liver disease) [144], the strongest associations with liver failure and cirrhosis were the age at which patients first used MTX and the time since initiation of MTX therapy. Serum AST and albumin were the only measures of hepatic function that were more likely to be abnormal in cases relative to controls but were as often normal as abnormal in cases one year before the onset of liver failure.

Two cases of reversible liver failure, one with idiopathic chronic hepatitis, in patients receiving low dose MTX for RA were reported by Clegg et al. [112] Kujala and co-workers reported a further case of reversible liver failure in a patient taking MTX for RA [116, 117]. In each of these three cases, liver function improved after MTX was discontinued. Both authors suggest that careful monitoring of patients undergoing long-term, low dose MTX treatment is important.

Obesity will cause fatty liver and raised triglycerides. More recently, Kent et, al. [143] reported that high body mass index, untreated hyperlipidemia and lack of folate supplementation correlated with elevation in serum of the liver enzyme aspartate aminotransferase based on a retrospective cohort study.

2.7.4.4 Risk Factors for Methotrexate Haematological Toxicity

Haematological toxicity of MTX includes leukopenia, thrombocytopenia, megaloblastic anaemia and pancytopenia. Pancytopenia secondary to low-dose MTX in RA patients has been reported [118, 119, 145]. Pancytopenia-related death has been reported due to myelosuppression, which led to sepsis or haemorrhage.

Numerous studies have identified risk factors that contribute to haematotoxicity. These include impaired renal function [146-151], elevated mean corpuscular volume (MCV) [152, 153], hypoalbuminemia [143, 146-148, 151], and concomitant medication [146-148, 151, 154, 155].

Weinblatt et al. compared six RA patients with MTX-associated haematological manifestations and compared them with 17 other RA patients receiving MTX and argued that raised MCV may be associated with haematotoxicity, perhaps though relative folate depletion [153]. Al-Awadhi et al. [152] conducted a case-control study to identify risk factors associated with pancytopenia occurring during low-dose MTX therapy within the decade 1981 to 1991 as ascertained by a survey of haematologists, dermatologists and rheumatologists in the Ottowa region. Relative to controls matched for duration of MTX therapy, the pancytopenia group was more advanced in age and more often displayed impaired renal function and elevated MCV The study also suggested that co-administration of trimethaprim-sulphamethoxisole, an antimicrobial combination that, like MTX, can interfere with folate metabolism, is also a risk factor. Maricic et al. reported the case of a 47 year old woman, who developed megaloblastic pancytopenia shortly after trimethoprim/sulfamethoxazole was added to her regimen.

Gutierrez-Urena et, al. [156] reviewed 68 pancytopenia cases in the medical literature published between 1980 to 1995 and also described two cases from their own experiences. They estimated that pancytopenia occurs in 1 to 2% of patients receiving low-dose MTX therapy in RA. Many of the cases reported in their review had occurred before folate supplementation had become a recommended accompaniment of MTX therapy and their estimate of the incidence of pancytopenia may be an over-estimate relative to contemporary practice.

Notwithstanding, MTX haematoxicity is an important complication, which can be fatal and for which there are multiple risk factors that are suited to inexpensive computer-aided safety monitoring (renal function, MCV, serum albumin and cell counts for early recognition of adverse trends, reminders regarding folate administration and drug interaction alerts [trimethaprim-sulfamethoxisole]. Unpublished observations from the eRA clinic indicate a strong association between disease suppression and moderate reductions in leucocyte and platelet counts and increased MCV [157]. Accordingly, a balance between moderate reductions in cell counts and disease control may yield best results, thereby making computer-aided safety monitoring for safety and dose adjustments especially important.

2.7.4.5 Risk Factors for Methotrexate Gastrointestinal Toxicity

Gastrointestinal (GI) toxicity is the most common side effect in RA patients receiving low-dose MTX [110, 158-160], while haemorrhage, enteritis and death from intestinal perforation are rare. Nausea, vomiting, diarrhoea and ulcerative stomatitis are common unwanted effects. Supplementation with folic (or folinic acid) can be used to reduce the unwanted mucosal effects of MTX [161], but possibly at the cost of some reduction in efficacy [162].

Furst et, al. [159] performed a long-term prospective trial of 45 RA patients receiving MTX. They found that GI adverse effects occurred in 93% of patients during the trial period of 176 weeks. Bologna et, al. [160] reported after a long-term retrospective observation study of 453 RA patients treated with MTX, that GI effects are the most common adverse event (19.7%), and also a major cause of drug termination (5.7%). Hoekstra et, al. [126] conducted a study that analysed data from a 48 week randomised clinical trial on 411 RA patients treated with MTX. They found GI adverse effects are related to prior GI events (OR 1.81, P=0.02).

2.8 Decision Theory for Managing Drug Toxicity in Rheumatoid Arthritis

During the management of RA, assessing patients for drug toxicity is fundamental in decision-making. Clinicians often face the decision of whether to modify or maintain a patient's current treatment based on their assessment of the likely best outcome in terms of achieving desired effects while avoiding unwanted events. Decision theory can be used to explain this decision-making problem.

2.8.1 Conditional Probability

The process of deciding on a treatment option is based on the estimated probability of drug toxicity for the given decision alternatives. Probability is expressed on a scale from 0 to 1; a rare event has a probability close to 0, a very common event has a probability close to 1 [163].

$P[T]_{Mt} = P(T \mid Mt)$ = *probability that drug toxic effects occur for given patient under maintained treatment decision.*
$P[T]_{Mf} = P(T \mid Mf)$ = *probability that drug toxic effects occur for given patient under modified treatment decision.*

2.8.2 Decision Tree

A decision tree is a method of representing and comparing the expected outcomes for each management alternative [163]. Constructing a decision tree helps the clinician to understand the decision problem and choose the management option most likely to benefit the patient.

Following a patient's assessment for drug toxicity, clinicians could either maintain the patient's treatment or modify treatment according to the patient's particular clinical state. Regardless of which option is chosen, the patient's ultimate outcome is determined by a set of chance events. The clinician has to estimate the probability of the outcome for the patient based on his or her knowledge and personal expertise.

Finally, a utility (expected value) has to be calculated for every outcome event. Figure 2.1 shows a decision tree for the decision-making process to decide whether to modify or maintain a patient's current treatment.

- *Decision alternatives:*
  a) *maintaining treatment (A_{Mt})*
  b) *modifying treatment (A_{Mf})*

- *Chance events:*
  a) *with toxic effects (P[T])*
  b) *without toxic effects (1-P[T])*

- *Outcome estimations(Utility):*
  a) *with toxic effects (U(T+))*
  b) *without toxic effects (U(T-))*

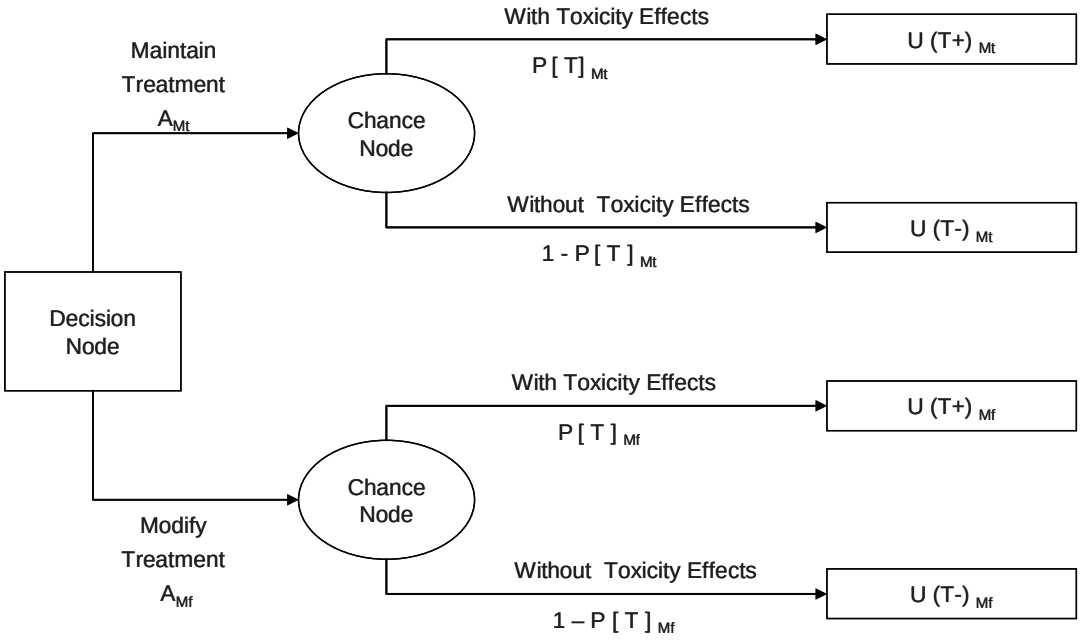


Figure 2.1 A decision tree comparing the two treatment alternatives

2.8.3 Decision Theory

Decision Theory refers to theories about how we should make decisions among the alternatives if we want to maximise expected utility [163]. Here I use Decision Theory to explain how to make decisions on whether or not to modify a treatment.

The decision theory = probability theory + utility theory (maximum expected utility) [4]

a) *Probability theory provides a description of how to estimate complex probabilities under uncertainty.*
b) *Utility theory refers to how to make the decision choice by determining the maximum expected utility of the decision outcomes.*

When deciding whether to modify a patient's current treatment or maintain a patient's treatment, there are two mutually exclusive patient outcome events for both decision alternatives: either the patient has drug-related toxic effects or the patient does not have drug-related toxic effects. Theoretically, clinicians' decision-making is affected by their perceptions of the probability of these events. Clinicians make a choice from the decision alternatives by estimating the probability that a particular event will occur. It is often a reasoned assessment based on their knowledge and expertise. The preference for whether to continue treatment or to modify the treatment depends on the outcome of the estimation.

$$U_{Mt} = P[T]_{Mt} * U(T+)_{Mt} + (1-P[T]_{Mt}) * U(T-)_{Mt}$$
$$U_{Mf} = P[T]_{Mf} * U(T+)_{Mf} + (1-P[T]_{Mf}) * U(T-)_{Mf}$$

The above equations calculate the expected utilities of the decision alternatives. By calculating the expected utility of maintaining treatment and the expected utility of modifying treatment, clinicians would choose the alternative with the highest expected utility.

2.8.4 Decision Threshold

While applying the decision theory, clinicians have to estimate P(T | Mt) and P(T | Mf), and then choose the treatment options with the maximum expected utility based on the calculation of U_{Mt} and U_{Mf}. If the expected utility for maintaining treatment is higher than for modifying treatment, clinicians will choose to maintain the treatment. On the other hand, if the expected utility for modifying treatment is higher than for maintaining treatment, clinicians will choose to modify the treatment. However, if the expected utility for maintaining treatment is the same as for modifying treatment, this means decision-making reaches a decision threshold. In other words, under P(T | Mt) and P(T | Mf), the expected utilities for maintaining treatment and modifying treatment are no different. Clinicians will have no preference between the two decision alternatives. Figure 2.2 shows that under one set of conditions, with the probability of drug toxicity under the modified treatment option being $P[T]_{Mf}$ and the probability of drug toxicity under the maintaining treatment option being $P[T]_{Mt,}$ as depicted, the expected utility U_{Mf} is greater than U_{Mt}; therefore, theoretically, other factors being equal, modifying treatment is the better option to take. Under another set of conditions, with the probability of drug toxicity under the modified treatment option being $P[T]_{Mf}$' and the probability of drug toxicity under the maintaining treatment option being $P[T]_{Mt}$', the expected utility U_{Mf}' is the same as U_{Mt}'; therefore, decision-making reaches decision threshold, and the values of the $P[T]_{Mf}$' and $P[T]_{Mt}$' are called threshold probabilities.

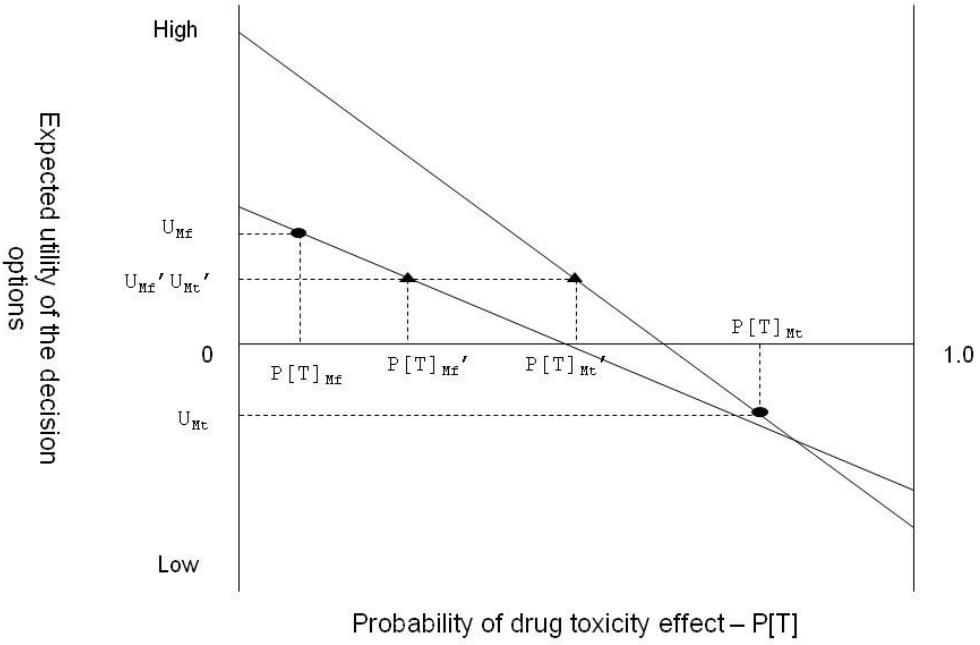


Figure 2.2 Expected Utility for maintaining treatment (AMt) and modifying treatment (AMf) options

3 Study Objects and Hypotheses

EBM promotes the use of high quality evidence in clinical decision-making processes. For example, CPGs aim to improve the quality of clinical decision-making by synthesising best evidence into management plans. However, gaps exist between optimal practice and actual practice. Firstly, clinicians often have difficulty in adopting complex CPGs in practice because recourse to reference material impedes workflows that rely on direct action using clinician recall. Secondly, standard CPGs cannot address all aspects of patient care. They are largely limited to generic recommendations, which cannot address the myriad of contingencies encountered in practice. Thirdly, time constraints in accessing the latest information, and the habituation and inertia of professional behaviour militate against the incorporation of new evidence into routine practices.

CDSSs can assist clinical decision-making through the delivery of CPGs at the point of care, through the provision of appropriate recommendations, reminders and alerts in response to entry of clinical and laboratory inputs and chronological assessment. Despite strong evidence that CDSSs can improve compliance with best practice and patient safety, they are used little in routine clinical settings. Obstacles to the wider use of CDSSs include the challenges of development and adaptation of guidelines for electronic implementation, and the efficient integration of CDSSs into clinical workflows. Finally, the extent to which CDSSs will impact positively in various clinical settings is yet to be established. This research is designed to explore the application of CDSSs in a clinical setting, where a relatively ordered approach to the clinical management of a complex chronic disease such as RA has already been established.

3.1 Objectives

1. To assess and understand the complexity of RA management
2. To outline the business requirement of the CDSS for assisting clinical decision-making

3. To establish comprehensive RA management rules by incorporating relevant evidence from the literature and expertise from domain experts
4. To define a computer interpretable model of the RA management rules
5. To create a MTX toxicity prediction model utilising the best evidence from relevant literature and clinical expertise
6. To identify the opportunities for incorporating the CDSS into the clinic workflow
7. To conduct a questionnaire to evaluate the compliance of the RA management rules; and to thereby assess subsequent clinical acceptance and effectiveness of the CDSS

3.2 Hypotheses

1. The conscientious use of best evidence in clinical decision-making can be achieved through application of Knowledge Acquisition processes, in order to facilitate the development of CPGs
2. A computer interpretable model can be established for highly complex CPGs
3. The CDSS guidance concurs with interpretation of the RA management rules for dosage adjustment by clinicians experienced in their application and accepting of the rules
4. More complex CPGs are associated with low compliance using manual approaches regardless of high guideline acceptance

4 Developing a Knowledge-based CDSS

Understanding the domain problem and then acquiring and representing the knowledge to solve the problem are fundamental processes in developing an intelligent knowledge-based system. Hence, developing a CDSS to assist clinical decision-making depends on an understanding of the clinical decision-making, which requires elicitation of extensive clinical knowledge.

During the RA management, clinical decision-making necessarily draws on extensive domain knowledge and up-to-date medical evidence. Developing a knowledge-based CDSS, with the features of delivering complex RA management rules, involves multiple complex processes. This study employed Knowledge Engineering as a technique underpinning the CDSS development for the eRA clinic. Knowledge engineering is the technique of building intelligent knowledge-based systems such as CDSS [164]. It includes three main processes, which are (1) problem assessment, (2) data and Knowledge Acquisition, and (3) system implementation (Figure 4.1). Facilitating these processes during the development of CDSSs contributes to the ultimate effectiveness of the system.

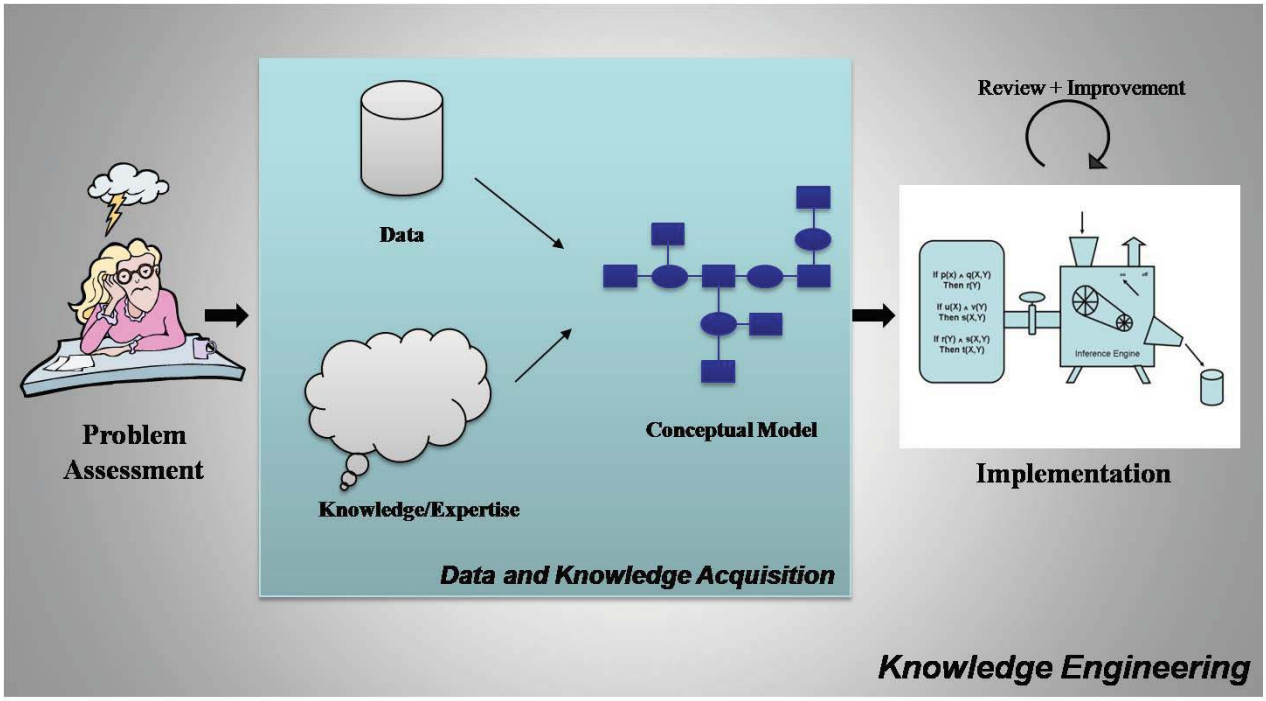


Figure 4.1 Knowledge Engineering Processes

Knowledge Acquisition is fundamental to Knowledge Engineering and is generally the rate limiting step in building a knowledge-base system. This process is comparable to the combination of requirements analysis phase and conceptualisation phase of the Software Development Life Cycle (SDLC). It is the process to gain the understanding of the problem for which the software system is to solve. Knowledge within a particular domain can be acquired through consulting human experts within the domain, and understanding their business processes and associated rules. Using graphical flow charts is a natural way to represent knowledge. Flow charts can be easily understood by humans; therefore they can be verified by the human experts.

Knowledge acquired from human experts and relevant literature provides the substrate for constructing a conceptual model which represents knowledge. A conceptual model is a formal structure for describing knowledge using symbols. Symbols represent the concepts of knowledge and the implicit and explicit relationships between them. A conceptual model can be established by characterising the data of interest, context, key words, rules and relationships. Constructing a conceptual model is one of the crucial phases in the SDLC. Figure 4.2 schematically illustrates the major steps in building a knowledge-based CDSS.

One of the key focuses of this study is Knowledge Acquisition. The objective of applying knowledge Acquisition in this study is (a) to identify the domain knowledge (clinical evidence, clinical expertise, etc.), (b) to develop and explicitly represent the clinical rules for decision-making, (c) to establish the knowledge models, (d) to outline the clinical decision-making processes and (e) to analyse the clinical workflows.

At the early phase of the study, I outlined five key steps for the development of the knowledge-based CDSS. These five steps are (1) problem assessment, (2) Knowledge Acquisition, (3) evidence/knowledge establishment, (4) conceptual model development, and (5) CDSS implementation and evaluation. I also specified the key objectives for each step. The five steps and their objectives are listed as below:

1. Problem assessment

To identify problems/questions which the clinicians are trying to solve/answer during RA management

2. Knowledge Acquisition

To understand the underlying rationale of the clinical decision-making in RA management; to analyse the decision-making processes and the clinical workflow

3. Evidence/knowledge establishment

To define a knowledge-based CDSS with the functions of guiding eRA management decisions in response to defined contingencies, both with regard to disease suppression, toxicity and unwanted events monitoring (it includes explicitly establishing RA management rules and identifying risk factors in developing MTX toxicity and side effects in RA)

4. Conceptual model development

To establish a computer interpretable model for the complex RA management rules; to set up a drug toxicity prediction model for MTX within the regimen; to map the computer interpretable model and the drug toxicity prediction model into the clinical decision-making process

5. CDSS implementation and evaluation

To implement the CDSS; to evaluate the CDSS; therefore to determine which features have been effective or ineffective in solving identified problems

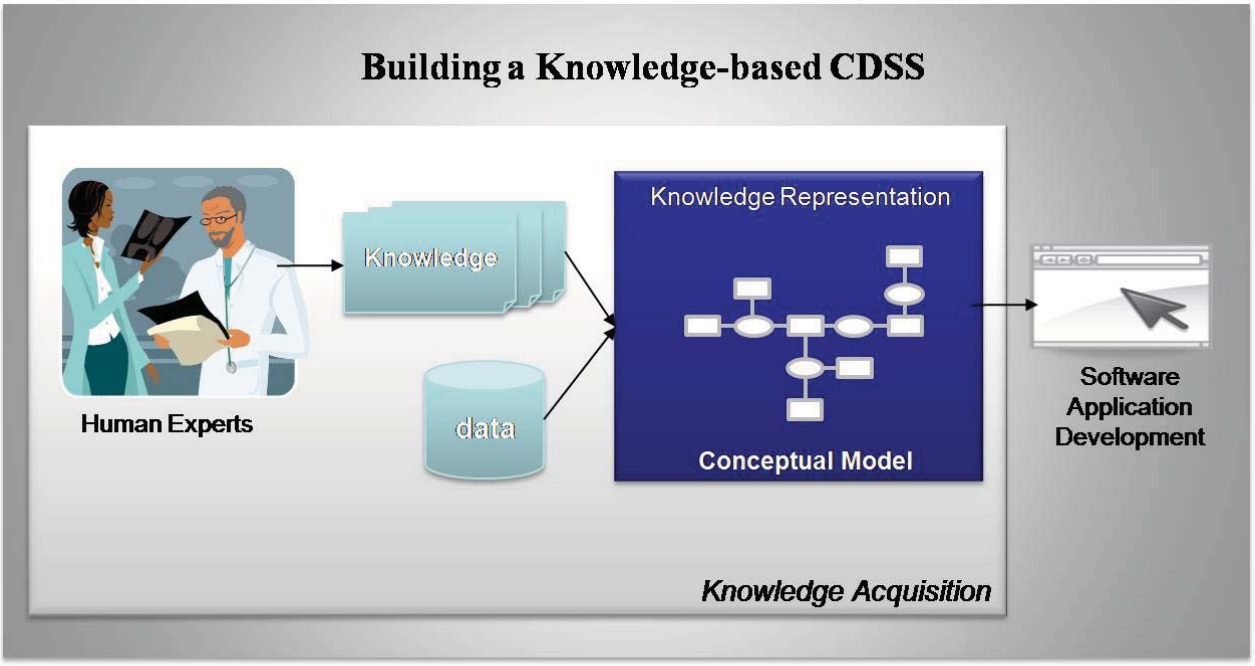


Figure 4.2 Knowledge Acquisition in building a knowledge-based CDSS

5 Knowledge Engineering the Management of Rheumatoid Arthritis in the eRA Clinic

Managing RA is a complex task because of the need to use combinations of DMARDs early for optimal disease control and long-term outcomes. MTX is one of the most widely used DMARDs. However it can cause potentially irreversible or even fatal ADRs. Best practice requires adjustment of dosages of medications and substitutions of medications according to a patient's response and tolerance. These factors demand the close monitoring of disease activity and of certain blood investigations that are used for safety monitoring, as well as consistently applied responses to abnormal findings. Therefore, a knowledge-based CDSS is needed to assist clinicians in managing RA better.

The study engaged Knowledge Engineering as a technique to gain understanding of knowledge within the RA management process, and then to elicit the knowledge underpinning the establishment of evidence-based CPGs, finally to develop a knowledge-based CDSS to assist clinical decision-making. This chapter details the Knowledge Engineering processes I applied during the study. It outlines the complexity of the RA management; analyses decision-making processes; explains the underlying rationale of decision-making in the domain; demonstrates the processes of establishing the evidence-based RA management rules; and finally describes the development of the knowledge models.

5.1 Problem Assessment

During the first 6 months of the Project, study focused on the Problem Assessment. In order to understand the complexity of RA management, and how the eRA clinic has been approaching management complexity during its practice, I started to perform comprehensive review of literature for current best evidence in managing RA patients, in conjunction with consulting the local clinicians for their expertise in decision-making.

Conducting a comprehensive literature review is one of the key components of the Knowledge Acquisition. By reviewing literature, evidence can be identified and categorised. I conducted an exhaustive literature searching using Medline provided by PubMed; Search terms included the Medical Subject Headings (MeSH) of 'Methotrexate', 'Arthritis, Rheumatoid', 'Drug Toxicity', 'Risk Factors', 'Risk Management' etc.

In the meantime, I observed the clinic consultations on a weekly basis. I consulted the local clinicians and clinic experts on a regular basis. The observations and consultations helped me to understand the underlying rationale of clinical decision-making in the domain. I also investigated the eRA clinic database to become familiar with the usage of clinical variables and data formats. In summary, I gained a basic understanding of RA management complexity and contingency during the Problem Assessment period.

5.1.1 Triple Therapy

Prompt treatment of RA is a key to minimising joint and tissue damage, and enhancing a patient's quality of life. The current RA management paradigm uses an intensive treatment combination that combines various DMARDs and biological agents to achieve remission. The eRA clinic incorporates this paradigm into its practice. Patients commence RA treatment with Triple Therapy (Table 5.1).

Theoretically, optimal treatment decisions in the management of a disease such as RA, yield maximum benefits to the patient with minimal drug toxic effects. In order to enhance the quality of decision-making, the eRA clinic practices EBM by incorporating current best evidence into its decision-making process. Clinicians who better manage risks for possible drug toxic effects while delivering acknowledged benefits of treatment can reduce the incidence of drug discontinuation; thereby, maintaining DMARDs at whatever dose is necessary to achieve clinical improvement with fewer drug toxic effects.

Table 5.1 Triple Therapy

1	methotrexate (MTX) 10 mg/week (with folic acid 0.5 mg/d)
2	sulfasalazine (SSA) (0.5 g/day then increase by 500 mg/d at weekly intervals to 1 g bd)
3	hydroxychloroquine (HCQ) (200 mg bd)

5.1.2 Dose Modification Protocol

The eRA clinic developed a Dose Modification Protocol (Table 5.2). This protocol is supported by clinical expertise and best evidence [165]. The intensity of treatment beyond the doses specified in the starting Triple Therapy regimen is increased when predetermined RA disease suppression criteria are not met (as defined in Table 5.2). Clinicians thus decide whether to adjust drug dosage or add additional agents according to the patient's response to the treatment.

The eRA clinic has incorporated the Dose Modification Protocol (Table 5.2) into its practice through a paper-based approach. Clinicians apply this protocol during the decision-making process to adjust therapy in order to achieve the treatment's desired effects. According to the protocol**,** if a patient's treatment is insufficiently effective as determined by a formal disease activity assessment; pre-determined dose adjustments will be made. If the patient has a satisfactory response to the therapy, then the patient's current therapy is maintained.

Table 5.2 Dose Modification Protocol

A. Early Morning Stiffness ≥ 30 minutes
B. Fatigue ≥30 mm
C. Joint pain ≥ 30 mm
D. Joint tenderness or pain on movement ≥ 2
E. Soft tissue swelling (joints or tendon) ≥2
F. Acute phase response (at least 1 of the following 2):
1. Erythrocyte sedimentation rate (ESR) ≥ 28 mm/hour,
2. C-reactive protein (CRP) ≥ 10 mg/L)
If there is a positive response to E & F <u>OR</u> positive response to E or F and 2 of A – D, drug dosage will be modified as defined in the treatment algorithm (refer to Figure 5.6)

5.1.3 Patient Assessment Process Analysis

After twelve weeks of observing the eRA clinic consultations plus interviews with local clinicians, I gained a working knowledge of the patient assessment process in the eRA clinic. The overall assessment process involves not only an assessment of the effectiveness of the treatment, but also an assessment of toxic effects associated with the drugs. The result of the patient assessment process leads to a decision-making of adjusting the patient's treatment.

The process of assessing a patient includes two components which are an assessment of disease activity and an assessment of drug tolerance. During a clinical consultation, the clinician assesses the patient's disease activity for treatment efficacy and any signs of drug toxicity to protect the patient's safety under its **current drug regimen**. Disease activity assessment involves reviewing relevant laboratory test results and checking disease activity associated symptoms. Drug tolerance assessment involves reviewing drug toxicity monitoring tests and enquiring regarding symptomatic adverse events. The clinician applies the paper-based clinical rules and acts by protocol accordingly to the results of the two assessments. The paper-based clinical rules and protocols are here referred to as **Triple Therapy** and **Dose Modification Protocol**. According to these rules, the clinician could adjust the patient's treatment with a **revised drug regimen**. For instance, if the patient can tolerate the therapy, clinicians may increase the drug dosage to achieve targeted treatment effects. If the patient's current drug therapy has been maximised but is insufficiently effective, the clinician can add additional DMARDs or biological agents into the drug regimen. On the other hand, if patient cannot tolerate the therapy (shows the sign of drug toxicity), the clinician can reduce or hold the suspected toxicity causing DMARDs or biological agents.

Based on my understanding of the process, I drafted a patient assessment process flow chart. Then, I submitted the flow chart to the eRA clinic experts for verification. Some minor changes were made by the experts. Figure 5.1 is the verified version of the RA patient assessment process. On the flow chart, paper-based rules and protocols refer to the Triple Therapy and the Dose Modification Protocol.

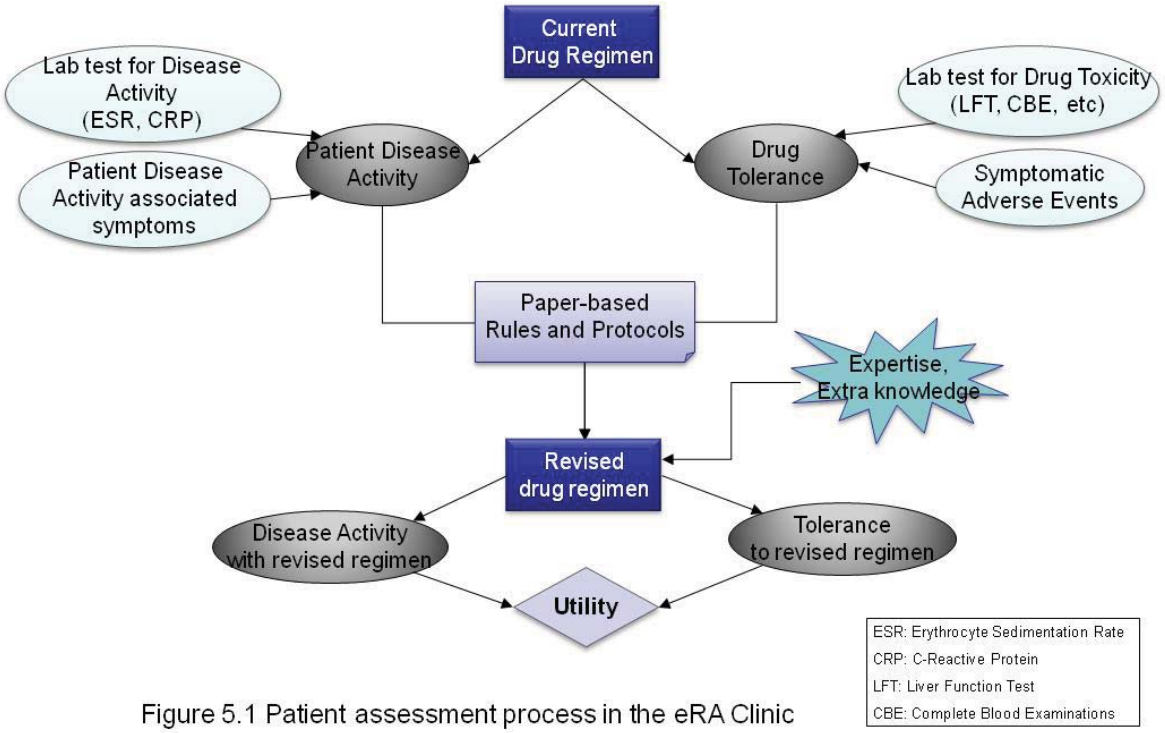


Figure 5.1 Patient assessment process in the eRA Clinic

5.1.4 Balance Disease Activity against Drug Tolerance

Figure 5.1 illustrates the process of assessing a patient in the eRA clinic. The assessment process seems being relatively straight forward. It is about how to make clinical decision on adjusting a treatment that balances the potential risks associated with therapy with its known benefits. However, the assessment process actually aims to maximise treatment efficacy and minimise drug-related toxicity (optimise the 'Utility').

A revised drug regimen with potentially increased 'Utility' is a desired treatment decision. The "Utility" hanging at the end of the patient assessment process represents the estimated outcome (patient benefits) which decides the final decision-making on drug regimen. In other words, the decision-making on how to revise the drug regimen depends on the estimated "Utility"; a better decision-making in revised drug regimen can increase patient benefits (Utility) measured by the combination of improved patient disease activity and the absence of drug toxic effects.

I found that the process has two important factors which drive the decision-making for revised drug regimen. Firstly, I found that the clinicians make treatment decisions by following the paper-based rules and protocols (refer to Triple Therapy and Dose Modification Protocol). However these rules give standard recommendations to assist clinical decision-making. Secondly, at the time of making decision in revised drug regimen, the clinicians often compromise the standard recommendations with their acquired personal preferences while estimating the 'Utility'. Therefore, paper-based rules and protocols might not be followed strictly during the decision-making of revised drug regimen. This could result in inconsistency in complying the standard rules and protocols.

5.1.5 Dose Modification Protocol Compliance Analysis

In order to further examine the degree of inconsistency in decision-making on revised drug regimen in the eRA clinic, I started to investigate the compliance rate of the Dose Modification Protocol at the early stage of the project while observing the clinical consultations. The eRA clinic had established a database that contains a broad range of patient data, including patient visit data, laboratory data, clinical data and patient treatment information. This database is a valuable source from which to perform secondary data analyses.

5.1.5.1 Protocol Compliance Rate

There were clinical data and laboratory data relating to 469 patient visits in the database at the time of analysis (September 2004). I performed a secondary data analysis to analyse compliance rate for the Dose Modification Protocol. I developed a computer program using C# programming language. The program automatically retrieves relevant data from the database, implements the Dose Modification Protocol and calculates the protocol compliance rate. As regards the results, there were a total of 101 patient visits in which the decision-making for revised drug regimen violated protocol recommendations. The protocol compliance rate was 78.5% and the protocol violation rate was 21.5%.

5.1.5.2 Protocol Violation Categorisation

The secondary data analysis showed the protocol compliance rate was 78.5%, which is mild to moderate degree of inconsistency in protocol compliance. Variation in compliance verified that the eRA clinicians employed additional personal expertise or preferences to complement the protocol according to the patient's particular clinical circumstances.

Base on the protocol violating cases, I further examined the case notes to explore the reasons for violating the Dose Modification Protocol. As regards the results, I identified the main causes as being related to drug-related toxicity or patients being

perceived to be at risk of drug toxicity. I then categorised the causes of protocol violation (Table 5.3) and counted the frequency of the each causes. Based on the analysis, I found that drug toxicity, drug side effects and drug toxicity risks were the top three reasons for protocol violation by the clinicians.

At the time the clinical decisions under analysis had taken place, drug toxicity rules had not been formulated which may explain the high rate of protocol violation. This deficiency was not appreciated until the CDSS project was undertaken and highlighted the need for detailed clinical guidelines to be formulated.

Table 5.3 Categorisation of protocol violation causes (Dose Modification Protocol)

Rank	Category	Detail
1	Drug toxic effects	abnormality detected in liver function test (LFT), complete blood examination (CBE), eye test for colour discrimination, etc.
2	Drug side effects	Symptoms such as nausea, hair loss, headache, irritability, etc.
3	Drug toxicity risks	pneumonia, urinary tract infection (UTI), upper respiratory tract infection (URTI), etc.
4	Special conditions	Undergoing antibiotic treatment, pregnant, etc
5	Patient reasons	Refused to comply, patient mistakes, etc.
6	Protocol exemptions	Patient in the early stage of the treatment (less than 6 weeks)
7	Special cases I	Dose modification criteria not fulfilled; but clinical evidence showed the disease was progressing
8	Special cases II	Symptoms were not RA related: joint tenderness and patient pain were due to Osteoarthritis or other medical conditions
9	Missing data	Laboratory results such as ESR and CRP were missing when applying protocol

5.1.6 Problem Assessment Outcomes

After spending 6 month on literature review of RA management, eRA clinic observation, and database investigation, I had gained a basic understanding of the fundamental decision-making and the ultimate goal of the RA management. The goal of the RA management is **to balance patient disease activity against drug tolerance, therefore to make optimised treatment decision towards increased patient benefits**. In order to achieve this goal, the eRA has established paper-based rules and protocols to standardise the decision-making on revised drug regimen. However my secondary data analysis found that the facts such as drug toxic effects, drug side effects and patient drug toxicity risks can lead clinicians to violate the standard recommendations, thereby leading to the inconsistency in clinical decision-making. Having gained insight into these issues, Knowledge Acquisition became the next step for incorporation of clinical evidence into the decision-making more completely, in order to improve the consistency and the quality of the decision-making.

5.2 Knowledge Acquisition

I started to apply Knowledge Acquisition processes as soon as the eRA management goal had been recognised. Since I had identified that the drug toxicity related issues caused the inconsistency in decision-making on revised drug regimen, I immediately began to perform a comprehensive literature review of drug toxicity in RA management. Meanwhile, I continued working closely with the clinicians and the clinic experts of the eRA clinic to clarify the knowledge within the decision-making processes.

During the management of RA, therapy-related toxic effects often cause treatments to be withheld and drugs to be discontinued or withdrawn, thereby, limiting the potential benefits of therapy. Identifying drug toxicity related symptoms and estimating the drug toxicity risk factors efficiently can prevent patients from suffering serious drug toxicity events. Clinicians therefore can revise patients' therapy based on these estimations. It is important that these decisions be orderly and based on best evidence if dosage adjustments are to yield consistently the best balance between efficacy and reduced risk for unacceptable and dangerous unwanted events. Also distinctions need to be made between uncomfortable, non-threatening nuisance effects which impose little risk to long-term health and serious, potentially irreversible or even fatal organ-threatening or life-threatening events.

5.2.1 Categorise Evidence - Risk Factors for Methotrexate Toxicity

Defining risk factors can be useful for quantitatively predicting the likelihood of developing drug toxicity in RA [70, 71]. Identifying risk factors helps planning for prevention of toxicities and gives clinicians the opportunity to apply appropriate medical interventions in time to avoid serious toxicity. Some studies have suggested that early recognition of risk factors for drug dosage adjustments or drug withdrawal may avoid serious and even fatal outcomes [70, 89].

I systematically reviewed a total of 23 studies from 1987 to 2004 for the risk factors associated with MTX in RA (refer to chapter 2.7.4 for details). I constructed a table of

risk factors that have been suggested as being associated with MTX toxicity. It summarises the reviewed studies (refer to appendix: tables of MTX toxicity risk factors) by detailing types of studies, analytical methods and identified risk factors, etc. Based on this table, I adopted the evidence grading methodology defined by Shekelle *et al* [166]. The categorisation is defined according to classification schemes based on the potential for bias that may influence the results (Table 5.4). As such the highest category evidence (Ia) is represented by meta-analyses of randomised control trials. And it provides support for the highest strength of recommendation (A). By contrast, evidence from expert committee reports or opinions or clinical experience of respected authorities falls in the weakest category evidence (IV).

According to their defined categories of evidence, I classified and graded risk factors associated with MTX toxicity in RA from my literature review. Table 5.5-1 summarises the common risk factors for MTX toxicity and their associated evidence category. The common risk factors include advanced age, impaired renal function and lack of folate supplementations. These common risk factors are dose related or affected by impaired drug clearance suggested a direct pharmacological effect on susceptible patients.

Table 5.5-2 summarises the risk factors for MTX pulmonary toxicity and their associated evidence category. Table 5.5-3 summarises the risk factors for MTX hepatic toxicity and their associated evidence category. Table 5.5-4 summarises the risk factors for MTX gastrointestinal toxicity and their associated evidence category. Table 5.5-5 summarises the risk factors for MTX haematological toxicity and their associated evidence category. These risk factors include not only direct drug effect related risk factors, but also risk factors related to aggregation of pre-existing diseases or conditioned by underlying organ specific diseases.

According to the above categorisation, there is strong evidence that risk factors such as lack of folate supplementation, impaired renal function, prior gastrointestinal events, alcohol abuse and increased dosage are associated with MTX toxicity in RA.

The pie chart (Figure 5.2) gives an overview of the evidence category distribution of the studies on MTX risk factors. From the 23 studies which had identified the risk factors for MTX toxicity in RA, six studies (25% of the studies) recommended the risk factors with strong evidence (category II or plus). The remaining 17 studies (75% of the studies) had relatively weak evidence to support their recommended risk factors for MTX toxicity in RA.

Table 5.4 Categories of evidence and strength of recommendation

Category of evidence:
Ia – evidence for meta-analysis of randomised controlled trials Ib – evidence from at least one randomised controlled trial IIa – evidence from at least one controlled study without randomisation IIb – evidence from at least one other type of quasi-experimental study III – evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies IV – evidence from expert committee reports or opinions or clinical experience of respected authorities, or both
Strength of recommendation:
A - directly based on category I evidence B – directly based on category II evidence or extrapolated recommendation from category I evidence C - directly based on category II evidence or extrapolated recommendation from category I or II evidence D – directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

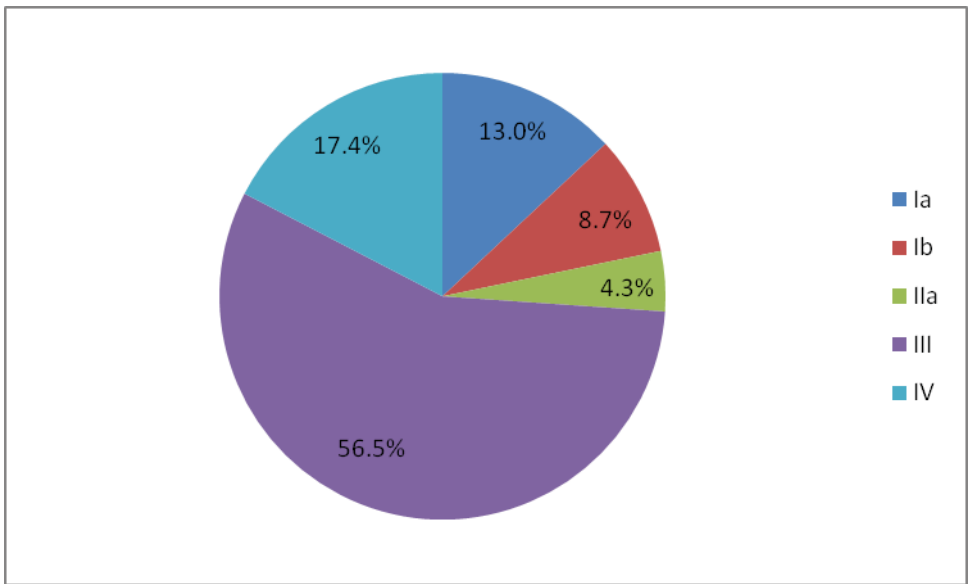


Figure 5.2. The evidence category distribution of the studies on MTX toxicity risk factors

Table 5.5-1 Common risk factors for MTX toxicity with associated evidence categories

Author(s)	Study Design	Common Risk Factor for MTX Toxicity	Evidence Category
McKendry, R.J. et al., 1993	Retrospective survey of 144 RA patients for 13 years	Advanced age	III
Buchbinder, R., et al., 1993	Retrospective review of 587 patients up to 1986	Advanced age	III
Wolfe, F. et al., 1991	Retrospective review of 235 RA patients from 1976 to1990	Advanced age	III
Rheumatoid Arthritis Clinical Trial Archive Group, 1995	A meta-analysis of 496 patients from 11 placebo controlled and comparative MTX clinical trials	Impaired renal function	Ia
Mielants, H., et al., 1991	Open prospective study of 92 RA patients	Impaired renal function	III
Morgan, S.L., et al., 1990	A 24 weeks, placebo-controlled, double-blind, trial of 32 patients	Lack of folate supplementation	IIa
Ortiz, Z., et al., 1998	A systematic review of 7 trails (147 patients)	Lack of folate supplementation	Ia
van Ede, A.E., et al., 2001	A 48 weeks randomized, double-blind, placebo-controlled trial of 434 RA patients	Lack of folate supplementation	Ib

Table 5.5-2 Risk factors for MTX pulmonary toxicity with associated evidence categories

Author(s)	Study Design	Risk Factor for MTX Pulmonary Toxicity	Evidence Category
Searles, G. et al., 1987	Case reports and a review of the literature	Smoking, pre-existing pulmonary diseases	IV
Golden, M.R., et al., 1995	case-review study of 125 RA patients from 1980-1989	Pre-existing pulmonary disease	III
Carroll, G.J., et al., 1994	case-control study of 12 patients	pre-existing lung disease	III
Alarcon, G.S., et al., 1997	case-control study of 29 patients from 1981 to 1993	Advanced age, smoking, rheumatoid pleuropulmonary involvement	III
Kremer, J.M., et al., 1997	Retrospective combined cohort review and abstraction form the English medical literature	Clinical features including shortness of breath, cough etc.	IV

Table 5.5-3 Risk factors for MTX hepatic toxicity with associated evidence categories

Author(s)	Study Design	Risk Factor for MTX Hepatic Toxicity	Evidence Category
Shergy, W.J., et al., 1988	Retrospective study of 538 patients from 1979 to 1988	Diabetes, obesity	III
Kremer, J.M. et al., 1989	A prospective study with baseline and sequential biopsy samples of 29 patients	Alcohol, obesity, dose, duration, elevated liver enzymes	III
Whiting-O'Keefe, Q.E. et al., 1991	A meta-analysis of 334 RA patients from 15 studies	Alcohol, dose	Ia
Walker, A.M., et al., 1993	Case-control study of 24 cases	Age, dose and duration, elevated liver enzyme, hypoalbuminemia	III
Kent, P.D. et al., 2004	Retrospective cohort study of 481 RA patients	Lack of folate, untreated hyperlipidemia, increased BMI	III
Hoekstra, M., et al., 2003	A randomise clinical trial of 411 RA patients for 48 weeks	Lack of folate, high BMI	Ib

Table 5.5-4 Risk factors for MTX gastrointestinal toxicity with associated evidence categories

Author(s)	Study Design	Risk Factor for MTX Gastrointestinal Toxicity	Evidence Category
Hoekstra, M., et al., 2003	A randomise clinical trial of 411 RA patients for 48 weeks	Prior gastrointestinal events	Ib

Table 5.5-5 Risk factors for MTX haematological toxicity with associated evidence categories

Author(s)	Study Design	Risk Factor for MTX Haematological Toxicity	Evidence Category
al-Awadhi, A. et al., 1993	Case-control study of 15 cases for 10 years	Impaired renal function, MCV, increased age	III
Weinblatt, M.E. et al., 1989	Retrospective analysis of 23 RA patients	Elevated MCV	III
Gutierrez-Urena, S., et al., 1996	Literature review + 2 cases report from 1980 to 1995	renal impairment, concomitant infection, concomitant therapy (including NSAIDs, trimethoprim /sulfamethoxazole), hypoalbuminemia	IV
Maricic, M. et al., 1986	1 Case report	Co-administration of trimethaprim-sulphamethoxisole	IV

5.2.2 Categorise Evidence - Methotrexate Toxic Effect

Identifying MTX toxic effects can be useful for preventing life threatening adverse drug reactions for RA patients on MTX treatment, thereby refining RA management for better patient outcomes. Identifying early signs of the toxic effects helps planning strategies for preventing toxicity and gives clinicians the opportunity to apply appropriate medical interventions in time in order to avoid serious toxicity. Some studies have suggested that understanding the prognostic factors of the drug-related toxic effects can influence the probability of maintaining a patient's on MTX treatment for a long period of time [110, 111].

I systematically reviewed a total of 23 studies from 1983 to 2000 for the MTX associated adverse events in RA treatment (refer to chapter 2.7.3 and chapter 2.7.4 for details). Based on my literature review, I constructed a table of MTX associated toxic effects in RA by specifying study titles, study designs and identified toxic effects, etc.; Table 5.6-1 outlines MTX pulmonary toxic effects; Table 5.6-2 outlines MTX hepatic toxic effects; Table 5.6-3 outlines MTX gastrointestinal toxic effects; table 5.6-4 outlines MTX haematological toxic effects. I once again applied the evidence grading methodology defined by Shekelle *et al* [166] to classify and grade these identified drug toxic effects with their associated evidence categories. According to this categorisation, there is strong evidence that folic acid and folinic acid reduce MTX gastrointestinal toxicity in RA. In addition, relatively strong evidence links MTX spoliated histological hepatic abnormalities with a subsequent hepatic fibrosis.

The pie chart (Figure 5.3) gives an overview of the evidence category distribution of the studies on MTX toxic effects. From the 23 studies which had identified the MTX toxic effects in RA, only 2 studies (9% of the studies) recommended the MTX toxic effects with strong evidence (category II or plus). The remaining 21 studies (91% of the studies) had relatively weak evidence to support their recommended MTX toxic effects in RA. This finding suggested that more high quality clinical trials are needed to investigate MTX toxic effects in RA. Thereby, strong evidence can be incorporated into clinical decision-making processes for better RA management.

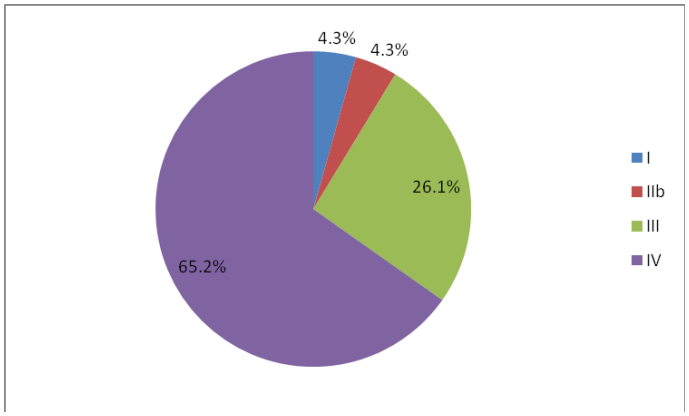


Figure 5.3. The evidence category distribution of the studies on MTX toxic effects

Table 5.6-1 MTX pulmonary toxicity with associated evidence categories

Author(s)	Study Title	Study Design	MTX Pulmonary Toxicity	Evidence Category
Grant W. Cannon et al., 1983	Acute lung disease associated with low-dose pulse Methotrexate therapy in patients with Rheumatoid Arthritis	Case report	Pulmonary disease	IV
Jame A. Engelbrecht, et al., 1983	Methotrexate pneumonitis after low-dose therapy for Rheumatoid Arthritis	Case report	Methotrexate Pneumonitis	IV
Pilar Barrera, et al., 1994	Methotrexate-related pulmonary complications in rheumatoid arthritis	Review	Pulmonary complications	IV
Gordon Searles, and Robert J.R. Mckendry, 1987	Methotrexate Pneumonitis in Rheumatoid Arthritis: Potential risk factors. Four case reports and a review of the literature	Case report & review of literature	Methotrexate Pneumonitis	IV
Matthew R. Golden, et al., 1995	The relationship of pre-existing lung disease to the development of Methotrexate pneumonitis in patients with Rheumatoid Arthritis	Retrospective cohort study	Methotrexate Pneumonitis	III

Table 5.6-2 MTX hepatic toxicity with associated evidence categories

Author(s)	Study Title	Study Design	MTX Hepatic Toxicity	Evidence Category
Ahern M.J. et al., 1998	Methotrexate hepatotoxicity: What is the evidence	Commentary	Fibrosis	IV
Jenny Heathcote, 1996	The significance of AST changes in patients with Rheumatoid Arthritis treated with Methotrexate	Editorial	Elevated AST	IV
James H. Lewis, 1997	Monitoring for Methotrexate Hepatotoxicity in Patients with Rheumatoid Arthritis: Another hepatologist's perspective	Editorial	Elevated AST, ALT	IV
Stanley L. Bridges, Jr. et al., 1989	Methotrexate-Induced liver abnormalities in Rheumatoid Arthritis	Editorial	Hepatic fibrosis	IV
Michael E. Weinblatt et al., 2000	Serious Liver disease I a patient receiving Methotrexate and Leflunomide	Case report	Early cirrhosis	IV
William J. Shergy, et al., 1988	Methotrexate-Associated Hepatotoxicity: Retrospective analysis of 210 patients with Rheumatoid Arthritis	Retrospective study	Hepatotoxicity	III
Joel M. Kremer et al.,1989	Liver Histology in Rheumatoid Arthritis patients receiving long-term Methotrexate therapy	Prospective study	Mild fibrosis	III
Quinn E. Whiting-O'Keefe et al., 1991	Methotrexate and histologic Hepatic Abnormalities: A meta-analysis	Meta-analysis	Hepatic fibrosis	IIb
Alexander M. Walker et al., 1993	Determinants of serious liver disease among patients receiving low-dose Methotrexate for Rheumatoid Arthritis	Prospective study	Serious liver diseases	III
Christine A. Phillips et al., 1992	Clinical Liver Disease in Patient with Rheumatoid Arthritis taking Methotrexate	Case report	Hepatic fibrosis/cirrhosis	IV
Daniel O. Clegg et al., 1989	Acute, reversible hepatic failure associated with Methotrexate treatment of Rheumatoid Arthritis	Case report	MTX related chronic hepatitis	IV
Kujala, G.A., et al., 1990	Hepatitis with bridging fibrosis and reversible hepatic insufficiency in a woman with RA taking Methotrexate	Case report	chronic hepatitis/fibrosis	IV

Table 5.6-3 MTX gastrointestinal toxicity with associated evidence categories

Author(s)	Study Title	Study Design	MTX Gastrointestinal Toxicity	Evidence Category
Zulma Ortiz et al., 1998	The efficacy of Folic Acid and Folinic Acid in reducing Methotrexate gastrointestinal toxicity in Rheumatoid Arthritis. A meta analysis of randomised controlled trials	Systematic review of RCTs	GI and oral side effects	I

Table 5.6-4 MTX haematological toxicity with associated evidence categories

Author(s)	Study Title	Study Design	MTX Haematological Toxicity	Evidence Category
Adel Al-Awadhi et al., 1993	Pancytopenia associated with low dose methotrexate therapy. A regional survery	Retrospective study	Pancytopenia	III
Sergio Gutierrez-Urena, et al., 1996	Pancytopenia secondary to Methotrexate therapy in Rheumatoid Arthritis	Case report & review of literature	Pancytopenia	IV
Bernhard Lang et al., 1991	Low dose Methotrexate therapy for Rheumatoid Arthritis complicated by Pancytopenia and Pneumocystis carinii Pneumonia	Case report	Pancytopenia	IV
Kevat S.G. et al., 1988	Pancytopenia induced by low-dose Methotrexate for Rheumatoid Arthritis	Case report	Pancytopenia	IV
Barrie Mayall et al., 1991	Neutropenia due to low-dose methotrexate therapy for psoriasis and rheumatoid arthritis may be fatal	Retrospective review of medical records	Neutropenia	III

5.2.3 Evidence-based Drug Toxicity Management in the eRA Clinic

In the eRA clinic, the patient's disease activity assessment evaluates the treatment benefits, while the patient's drug-related toxic effects assessment considers the treatment risks. During the RA assessment process, there are multiple variables involved in the evaluation of both the treatment efficacy and the drug-related toxicity that can contribute to a decision on whether to adjust a specific treatment. Variables include standardised assessment indices, such as disease activity score (DAS) and other clinical and laboratory variables. In the eRA clinic where treatment is designed to abrogate periarticular erosions and other radiographic signs of RA related joint damage, radiological findings are not a formal aspect of the assessments upon which treatment decisions are made as there may be lag time of several months before erosive damage is evident radio-graphically by which time the damage is often well-advanced.

5.2.3.1 Disease Activity Related Clinical Variables

The clinicians assess RA patients at standardised intervals (starting from every three weeks; extending to every six weeks after the third visit and every three months once remission has been achieved). The clinicians carry out regular clinical assessments of swollen and tender joints counts, patient assessed pain, well-being and fatigue (on 100mm visual analogue scores), duration of morning stiffness (minutes) and function (modified Health Assessment Questionnaire (mHAQ)) [167]. Laboratory investigations to evaluate the efficacy of treatment assess the acute phase response in the serum to inflammation with erythrocyte sedimentation rates (ESR) and C-reactive protein (CRP) as indices of disease activity. Assessments of the longer-term disease outcomes include radiographs of the hands and feet, bone densitometry at hip, spine and hands and quality of life (SF36, RAQoL).

5.2.3.2 Drug Toxicity Related Clinical Variables

Patients on DMARDs therapy are closely monitored for symptoms that may suggest drug toxicity. Regular blood tests are performed to detect the more serious toxic effects of DMARDs at an early stage (starting at every three weeks for 26 weeks; every six

weeks thereafter). At each clinic visit, the clinicians routinely require complete blood examinations (CBE) and liver function tests (LFT), which are used to assess haematological toxicity and hepatic toxicity of the treatments. Table 5.7 lists the major variables used for evaluating patient disease activity, drug-related toxic effects and longer-term effects of RA on skeletal structures.

Table 5.7 Variables for disease activity assessment, drug toxicity assessment and longer-term disease outcomes

Disease Activity	1. Morning stiffness (EMS) 2. Fatigue 3. Joint pain 4. Joint tenderness or pain on movement 5. Soft tissue swelling (joints or tendon) 6. Acute phase response Erythrocyte sedimentation rate (ESR) >= 28 mm/hour C-reactive protein (CRP) >= 10 mg/L 7. Disease Activity Score (DAS) 8. Physician assessment of disease activity 9. Patient assessment of disease activity
Drug-related Toxicity	1. Complete blood exam (CBE) 2. Liver function tests (LFT) 3. Urinalysis is performed as part of the monitoring intramuscular myocrisin (IM gold). 4. Serum creatinine is required as a baseline for methotrexate therapy for monitoring cyclosporine A nephrotoxicity 5. Pulmonary function test and Chest X-ray (CXR) are performed in smokers prior to treatment with methotrexate (MTX) 6. Annual assessment of retinal function using peripheral field and colour perception testing is undertaken during use of hydroxychloroquine (HCQ)
Longer-term Effects	1. X-rays of hands and feet (annually) 2. Bone Densitometry (6 monthly)

5.2.3.3 Clinical Routine Surveillance for Drug Toxicity

The eRA clinic applies Triple Therapy [methotrexate (MTX), sulfasalazine (SSA) and hydroxychloroquine (HCQ)] to RA patients from the time of diagnosis. Drug toxicity and nuisance side effects associated with, Triple Therapy or its components include effects on the lungs, blood cells, liver, gastrointestinal tract and retina. Identifying drug toxicity risk at an early stage and incorporating the risk into clinical decision-making is an important aspect of safety management.

The eRA clinic has been establishing and maintaining its surveillance list for drug toxicity related symptoms and abnormal laboratory findings. This information elicited through consulting the clinicians, which is sought routinely by pro forma at the eRA clinic and is relevant to Triple Therapy and its components, is summarised in Table 5.8. According to these listed nuisance events and toxicity, I found that the MTX related toxicity events align well with the identified MTX risk factors and toxicity events from my comprehensive literature review (Table 5.5-1 –Table 5.5-5). It suggests that the eRA clinic has been aiming to incorporate evidence-based risk factors and events for MTX toxicity into its daily practice. Apart from the evidence-based risk factors, most parameters listed it Table 5.8 are nuisance side effects but these, if left untreated, may evolve into symptoms of more serious toxicity so in themselves represent risk factors for serious toxicity.

Table 5.8 Routine surveillance for nuisance events and toxicity associated with components of Triple Therapy in the eRA clinic

Methotrexate	Sulfasalazine	Hydroxychloroquine
fever	fever	fever
weight loss (more than 4kg)	weight loss (more than 4kg)	
feeling unwell	feeling unwell	feeling unwell
headache	headache	headache
unusual fatigue	unusual fatigue	unusual fatigue
swollen glands		
loss of appetite	loss of appetite	
skin rash	skin rash	skin rash
loss of hair		
unusual bleeding	unusual bleeding	unusual bleeding
stuffy nose / sinusitis		
sores in the mouth	sores in the mouth	
cough / phlegm		
shortness of breath	shortness of breath	
wheeze		
heartburn / acid reflux	heartburn/ acid reflux	heartburn/ acid reflux
stomach pain or cramps	stomach pain or cramps	stomach pain or cramps
nausea	nausea	nausea
vomiting	vomiting	vomiting
diarrhoea	diarrhoea	diarrhoea
dark stools (bowel movement)		
blood in stool		
problems with urination	problems with urination	
abnormal vaginal bleeding		
dizziness		dizziness
any new health problem	any new health problem	any new health problem

Methotrexate	Sulfasalazine	Hydroxychloroquine
any new drug prescription	any new drug prescription	any new drug prescription
any discontinued drug	any discontinued drug	any discontinued drug
more than 2 alcoholic drinks / day		
problems with thinking		
problems with memory		
	depression - feeling blue	
	anxiety - feeling nervous	
	abdominal bloating	abdominal bloating
	problems with smell	
	problems with taste	
	problems with hearing	problems with hearing
		other skin problems
		other eye problems
		ringing in the ears
	sensitivity to sulphur-containing compounds	
a history of alcohol abuse		
impaired renal function		
impaired liver function	impaired liver function	
impaired lung function		
anaemia, leukopenia, neutropenia	anaemia,leucopenia,neutropenia	thrombocytopenia

5.3 Establish the Evidence-based RA Management Rules

Practising the principles of EBM relies on the rules of evidence and research. The eRA clinic promotes systematic and consistent treatment for each RA patient. Practice has been made more orderly and evidence-based by applying knowledge gained from clinical trials to patient care to develop clinical protocols and rules for patient management.

The eRA clinic has been establishing RA management guidelines aimed at improving and standardising clinical decision-making. Clinicians apply paper-based rules and protocols (**Triple Therapy** and **Dose Modification Protocol**) during an assessment of the patient before determining a recommended drug regimen. There are recognised limitations of paper-based rules and protocols, namely that they reflect general population standards for treatment and monitoring and may need to be tailored to the circumstances of an individual patient. For example, for the individual patient, some recommendations might seem too intensive, while others might be too conservative. While applying guidelines, a physician will often incorporate his or her expertise, extra knowledge, preferences and prejudices into the decision-making process, complementing standard rules and protocols according to the individual patient's medical condition. These modifications are not necessarily well-grounded and are an important source of variability in practice.

The eRA clinic has had an eight year experience with the implementation of **Triple Therapy** and **Dose Modification Protocol** for disease control and has established the general utility of its therapeutic algorithm [168]. By contrast, prior to the present study, formal rules for modification of treatment because of out-of-range blood results had not been articulated. A discretionary decision to violate eRA guidelines often depends on an estimate of the patient's toxicity risks based on laboratory data. It was therefore considered important to address this source of variability.

The identified clinical evidence from the literature review and the elicited clinical expertise from the eRA clinic forms a solid foundation to further establish and

maintain pertinent evidence-based CPGs, and consequently to incorporate the CPGs into daily clinical practice. With my assistance, the establishment of RA management rules was undertaken to assist clinicians in consistent, sound decision-making, therefore to formalise the decision-making process.

During the Knowledge Acquisition in the eRA clinic, the clinic consultations were observed. Interviewing/consulting the clinicians facilitated the process and benefited the thorough understanding of the domain knowledge. The eRA clinic experts used think-aloud strategy to verbalise their judging processes for a specific patient case. During the interviews, I used the transcripts to record the reasoning behind their decisions. I also pinpointed various types of knowledge surrounding the decision-making, such as rule sets, attributes, and relationships. As regards results, the clinical decision-making processes and underlying rationale of clinical decision-making were elicited. Based on the transcripts, I undertook further analysis to determine what clinical data were applicable to decision-making.

I created numerous draft versions of flow charts recording the clinical decision-making process. I also drafted flow charts for the RA management rules. The clinical experts from the eRA clinic were also engaged in the process during this period, especially during the period of verifying sketches of the flow charts. As regards results, the study has established two sets of evidence-based RA management rules; they are (a) **Rules for Changes in Dose/Agent**, and (b) **Drug Toxicity Monitoring rules**.

The development of these RA management rules reinforces standardised practice with consistent treatment. The eRA management rules incorporate both the best available evidence from the literature and the clinical expertise and experience within the eRA clinic. Participating clinicians can use them to make clinical decisions in adjusting therapy to achieve pre-defined levels of treatment response and with due regard to the tolerance of the patient to component medications in the treatment regimen.

5.3.1 Drug Toxicity Monitoring Rules

Developing Drug Toxicity Monitoring Rules can standardise patient monitoring of drug-related toxicity. It can also formalise clinical decision-making by incorporating the best evidence from relevant literature and clinical expertise. Therefore to prevent drug-related toxicity effectively and also reduce practice variation. The establishment of the Drug Toxicity Monitoring Rules started from mid 2005. The development consisted of methods such as identifying the evidence from the literature review and consulting the local clinical experts in the eRA clinic.

According to the literature review, risk factors such as lack of folate supplementation, impaired renal function, prior gastrointestinal events, alcohol abuse and increased dosage are associated with MTX toxicity in RA. Furthermore, according to the evidence categorisation, there is also strong evidence showing that MTX is associated with histological hepatic abnormalities such as hepatic fibrosis (refer to chapter 5.2.2). In addition, according to the secondary data analysis, concern regarding drug-related toxic effects such as abnormality detected in liver function test (LFT) and complete blood examination (CBE) was the major cause of protocol violation. Based on these facts, I began to engage the eRA clinicians to formalise the clinical decision-making rules on RA management for medication changes by incorporating best evidence, including not only that regarding identified risk factors and drug-related toxic effects, but also the relevant laboratory tests for drug toxicity monitoring.

An evidence-based expert consensus process was also used to create Drug toxicity Monitoring Rules. Rule scribbles written by the experts were collected and recorded (Figure 5.4). After I looked through the recorded rule scribbles, I found that Drug Toxicity Monitoring Rules are highly complex. They feature loops, complex state transition and time dependency. I therefore suggested the use of a flowchart to represent these rules. This was designed to allow clinicians to communicate more easily thereby facilitating refinements through exchange of opinions based b clearer concepts.

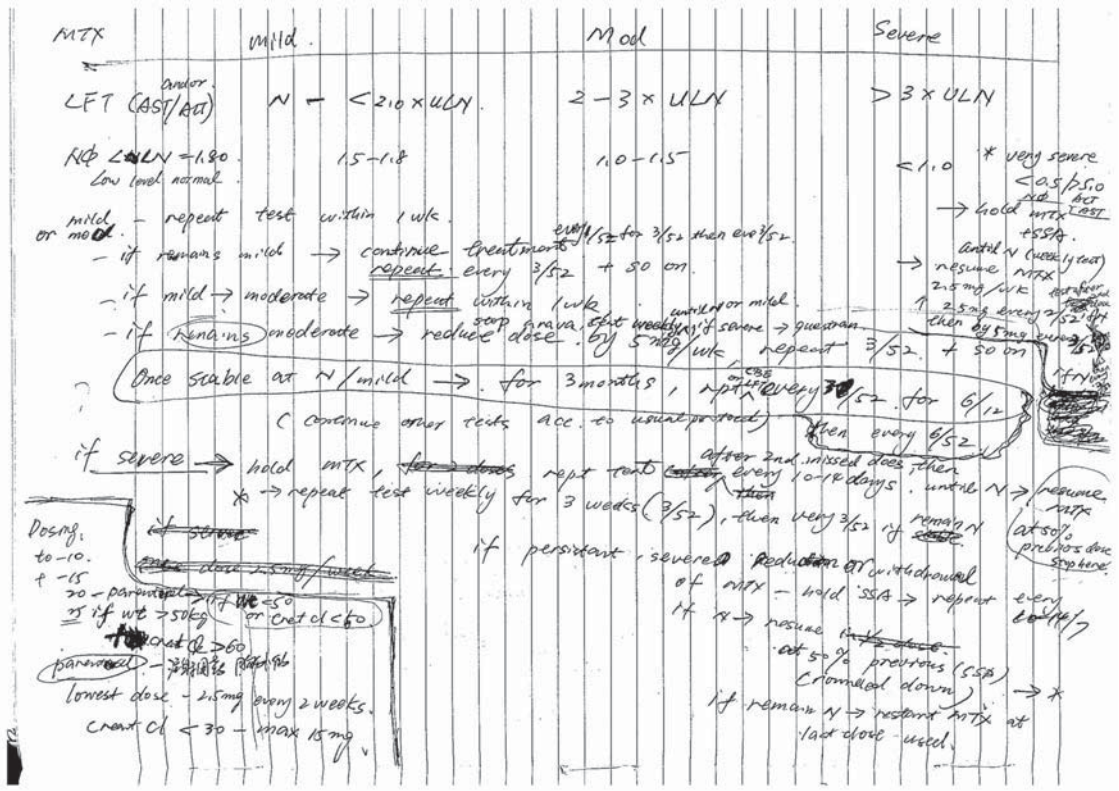


Figure 5.4 The recorded rule scribbles

I choose flowcharts as a form of graphical language to represent complex clinical rules such as the Drug Toxicity Monitoring Rules (Figure 5.5). Flowcharts allow clinical rules to be represented on a natural language-like pseudocode. As such, I believed that the complex rules are much better described in the form of flowchart. The relationships and flows between the corresponding rules are more clearly expressed in the diagram, and therefore the rule structure can be more easily understood.

The flowchart of the Drug Toxicity Monitoring Rules illustrates complexity and contingencies within the rule algorithm. It integrates neutrophil count which is a test within the CBE. It also integrated AST (aspartate transaminase) and ALT (alanine transferase) which are the tests within the LFT (liver function tests).

The eRA clinic had agreed on the decision of classifying the laboratory tests results (LFT and neutrophil count) into five ranks; they are normal, mild, moderate, severe and very severe toxicity (Table 5.9). Within the Drug Toxicity Monitoring Rules, mild

ranking and moderate ranking were combined together; therefore the Drug Toxicity Monitoring Rules included four sets of sub-rules (refer to Figure 5.5).

Table 5.9 The ranking of the laboratory test results in the eRA clinic (LFT and neutrophil count)

Laboratory Monitoring	Toxicity Ranking				
	Normal	Mild	Moderate	Severe	Very Severe
Liver Function Tests (LFT)	Within Normal range	Normal–>2×UNL	2×UNL–>3×UNL	>3×UNL	>5×UNL
Neutrophil Count	>1.8 $\times 10^9$/L	1.5–>1.8 $\times 10^9$/L	1.0–>1.5 $\times 10^9$/L	0.5–>1.0 $\times 10^9$/L	<0.5 $\times 10^9$/L
UNL: Upper Normal Limit					

The development of the Drug Toxicity Monitoring Rules was designed to assist the clinician in making optimal decisions. The rules provide more specific recommendations regarding patients in the events of drug toxicity. By classifying the ranking of the laboratory test results, the drug regimen can thus be modified consistently if the patient is likely to suffer drug toxicity. The agents that appear to cause significant unwanted effects can be revised or withdrawn.

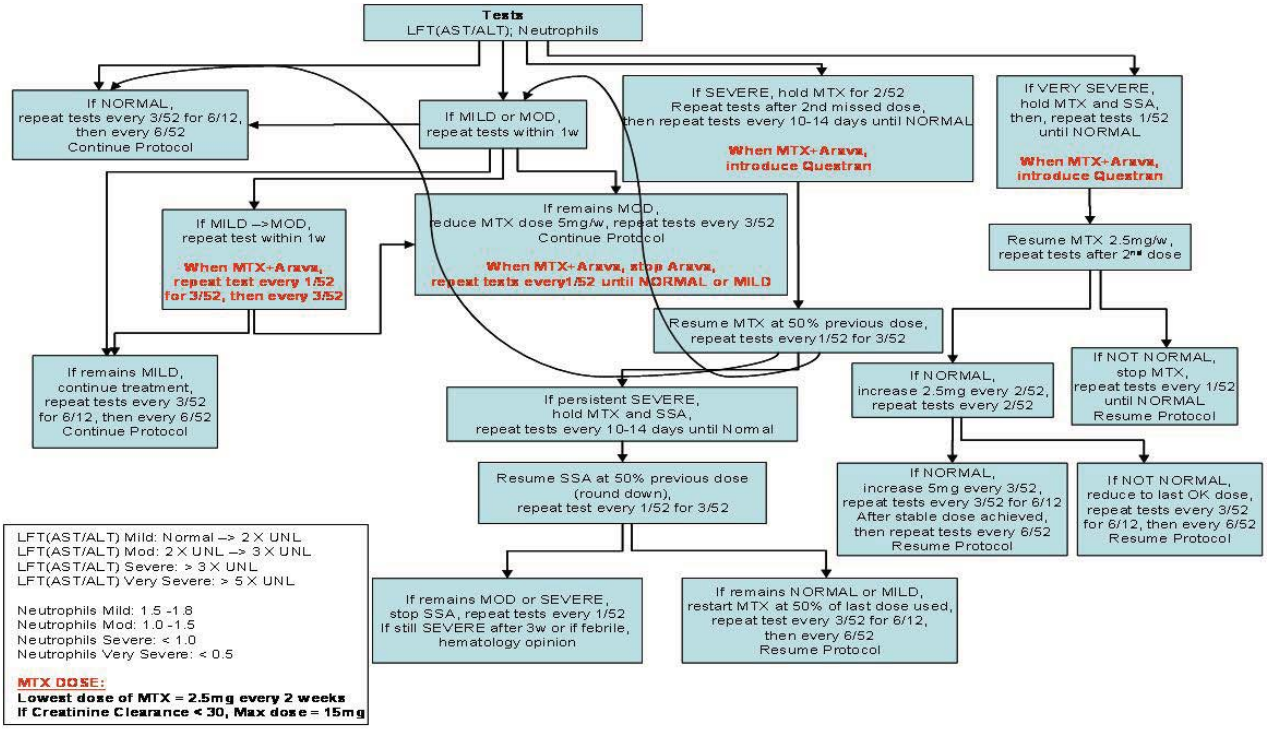


Figure 5.5 The eRA Toxicity Monitoring Rules

5.3.2 Rules for Changes in Dose/Agent

Rules for Changes in Dose/Agent were designed as a standardised set of recommendations for the introduction of Triple Therapy and for increasing the intensity of treatment through increases in doses and addition of further DMARDs if disease suppression criteria are not met. They are based on the premise that early remission-inducing interventions restore health and avoid or reduce long-term joint damage and disability. This protocol is in accordance with emerging worldwide treatment practices and extends existing trends through the application of more orderly and rigorous dose modification procedures.

Rules for Changes in Dose/Agent are contingent on the criteria for intensifying Treatment. These criteria reflect persistence of disease as evidenced by one or more swollen joints and increased acute phase reactants, or one of these plus two of: increased joint paint, stiffness, fatigue and more than 1 tender joint. According to the algorithm, clinicians could either increase the dosage of the drug agent or add an additional DMARD into the drug regimen depending on the patient's tolerance or point of progression through the algorithm.

Rules for Changes in Dose/Agent introduce drug agents into the drug regimen in a specified order (Table 5.10). As one of the agents in the Triple Therapy, MTX is always the first choice of the eRA clinic. In the initial period of the eRA clinic practice, myocrysin had preceded leflunomide in the order of application. With further experience with leflunomide, and in particular its more prompt therapeutic response rate relative to myocrysin, the order was reversed.

Table 5.10 Order of agents in the drug regimen of the Rules for Changes in Dose/Agent

Order	Agents
1	methotrexate (MTX)
2	sulfasalazine EC (Salazopyrin EN, SSA)
3	hydroxychloroquine (HCQ)
4	leflunomide (Arava)
5	intramuscular myocrisin (Gold)
6	cyclosporine A (Neoral)
7	TNF Blocker
8	azathioprine (AZA)

An evidence-based expert consensus process was also used to create Rules for Changes in Dose/Agent. Rule scribbles were collected and recorded during the group discussions with clinical experts from the eRA clinic. Then, I developed a flowchart for the Rules for Changes in Dose/Agent (Figure 5.6).

Rules for Changes in Dose/Agent integrated the identified drug toxicity risk factors and drug-related toxic effects from the literature review and evidence categorisation I performed earlier. Risk factors for MTX toxicity such as impaired renal function (measured by decreased creatinine clearance), increased age and increased dosage was incorporated into the rules. Rules for Changes in Dose/Agent also formalised the use of folic acid within the drug regimen. It supported the evidence from the meta-analysis of randomised controlled trials which showed the efficacy of folic acid in reducing MTX gastrointestinal toxicity in RA [128]. In additional MTX toxic effects such as GI side effects was included into the rules.

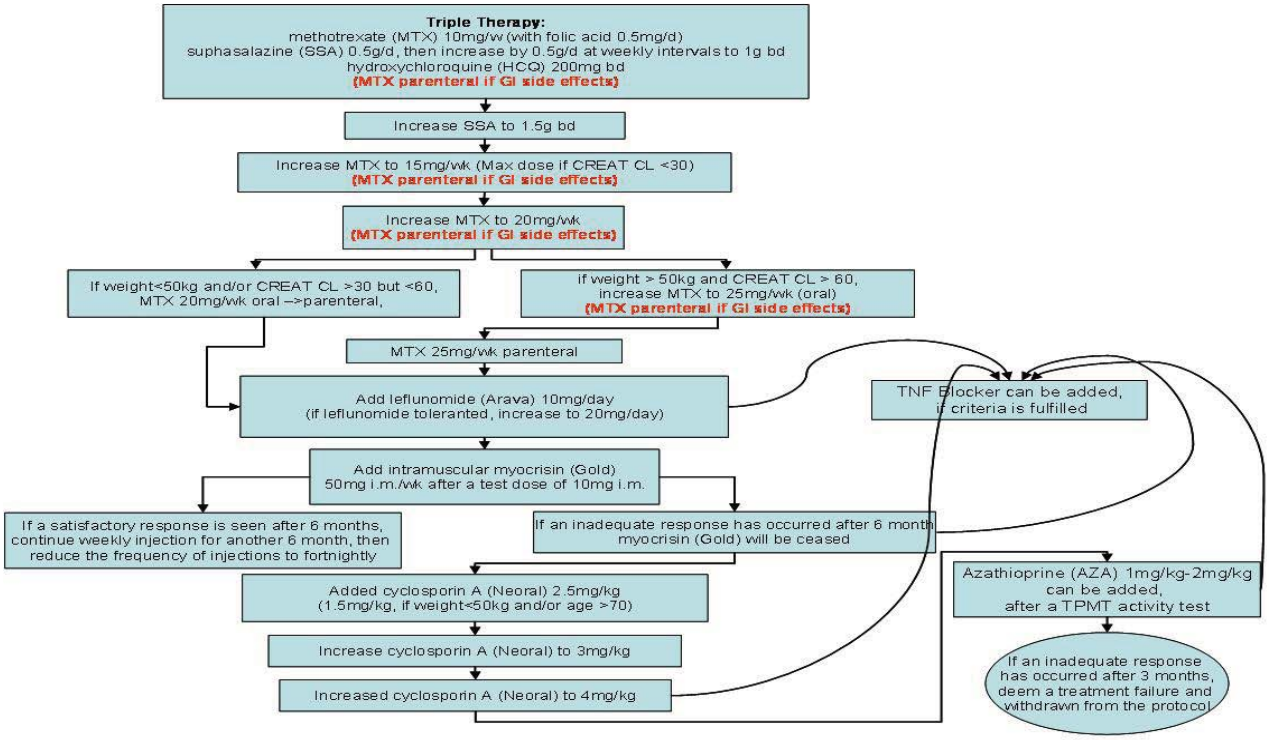


Figure 5.6 The eRA Rules for Changes in Dose/Agent

5.4 Knowledge Engineering Outcomes

From the literature, there were limited RA management rules for managing drug toxicity during RA management pathway, as well as introducing the sequence of different drug agents to control RA progression effectively and efficiently. Hence developing a comprehensive evidence-based RA management rules was drastic needed.

Knowledge Engineering had successfully identified the goal of the RA management, which is to balance patient disease activity against drug tolerance, therefore to make optimised treatment decision towards increased patient benefits. Through the Knowledge Acquisition processes, I established and categorised MTX toxicity risk facts and MTX toxic effects based on the literature review I performed earlier. Consequently, I engaged the eRA clinic; with my assistance, the eRA clinic developed the comprehensive RA management rules which integrated the best evidence and the local clinic expertise. The establishment of Drug Toxicity Monitoring Rules and Rules for Changes in Dose/Agent standardised the decision-making on revised drug regimen in the eRA clinic. Drug Toxicity Monitoring Rules gave specific recommendations regarding patients in the events of drug toxicity; and Rules for Changes in Dose/Agent focused on the specified order of introducing drug agents into the drug regimen.

The eRA-CDSS which was designed to implement the RA management rules can assist the eRA clinicians to comply with the rules. The eRA-CDSS has the potential to record the compliance data for audit. Thereby a more complete rules set with consequent elimination of variability in management can be established which allows outcomes from the eRA approach to contribute more meaningfully to knowledge about management, thereby creating a basis for refinement in management of RA.

6 Clinical Guideline Modelling

CDSSs can automate complex CPGs at point of care and deliver timely recommendations to clinicians thereby assisting clinical decision-making. Adopting CDSSs can reinforce guideline compliance hence practise of EBM. However, in order to deliver computerised clinical guidelines, human readable guidelines have to be represented into a format that can be interpreted by computers [49, 169].

The establishment of CPGs is fundamental to the development of guideline conceptual models that underpin CDSS implementation. This chapter explains the process of establishing conceptual models for the RA management rules including Drug Toxicity Management Rules and Rules for Changes in Dose/Agent. Based on the conceptual models, I further developed computer algorithms required for the CDSS application.

The exhaustive literature review on MTX toxicity had identified a complete list of risk factors for MTX toxicity and MTX toxic effects in RA. In addition, Bayes' Theorem and Bayes Net was studied in order to maximise expected utility while making decisions under uncertainty. Utilising Bayes' Theorem and Bayes Net to construct a drug toxicity prediction model allow unknown probabilities to be computed from known ones. This study has applied Bayes' Theorem and Bayes Net to establish drug toxicity prediction models for managing MTX toxicity in RA.

Furthermore, in order to achieve clinical efficiencies and wide clinical acceptance, CDSSs must not impact negatively on workflows. Thus, integration of CDSS into workflows is essential for the utility of CDSS in clinical decision-making. In this study a clinical workflow analysis was therefore performed to identify opportunities for the CDSS to be incorporated seamlessly into clinical management of RA.

6.1 Dynamic Characteristic of the RA Management Rules

Using flowcharts to represent the complex RA management rules, I have illustrated Drug Toxicity Monitoring Rules and Rules for Changes in Dose/Agent into sequential flows of decisions that match scenario with action (Figure 5.5, 5.6). However, due to the characteristics of RA management, the comprehensive RA management rules are highly complex; they feature loops, time dependency, state dependency and state transition. The state here stands for a patent's clinical condition at a specific point of time.

Using the Drug Toxicity Monitoring Rules as an example, this rule set features more complex rule structure. It consists of dynamic state transitions. The ancestor state within the rule set has multiple descendant states. As such it features state transition loops. This dynamic characteristic makes the rule set more complex to clarify. Therefore, conceptual models needed to be established for the RA management rules before implementing into the CDSS.

I drafted a sample dynamic model (Figure 6.1) to show a complete set of potential transitions between the normal state and the three toxicity states (previously defined in Table 5.9; mild toxicity and moderate toxicity were combined). Oval represents a patient state defined using LFT or neutrophils test results; and the colour coded lines linking the ovals represent the potential transitions from one state to another. Every state within the sample model has three ancestor states and three descendant states. As illustrated, there are total of 12 unique state transitions within the model.

A number of methods to support the computerisation of guidelines have been or are being developed by the Health Informatics community [170]. Tu et, al. [169] recommended a standard computer interpretable guideline structure. It used Decision Maps to represent static recommendations and 'guideline processes' to link the individual static recommendations together as a computational model. They had evaluated the proposed guideline structure by mapping GLIF, EON, PRODIGY3, and Medical Logic Modules into the proposed structures.

However, due to the dynamic characteristics (dynamic state transitions and transition loops) of the RA management rules, it remained challenging to work out the potential state transitions and transition loops of the RA management rules exhaustively. The pathways of the RA management rules are erratic when it progresses. Therefore Decision Tables cannot be linked by a simple 'guideline processes'. Further analysis to determine a complete set of pathways for the RA management rules is needed.

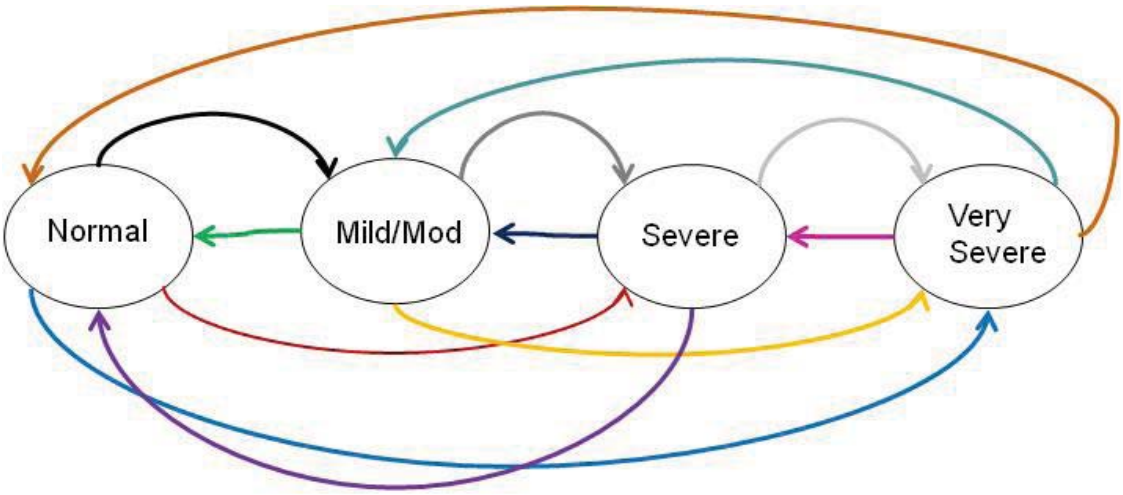


Figure 6.1 The complete transitions of a sample dynamic model

6.2 RA Management Rules Break Down

In order to clarify the Drug Toxicity monitoring Rules (Figure 5.5), I categorised the previously defined ranking of the laboratory test results into three toxicity events. They were mild-moderate event, severe event and very severe event. According to the three toxicity events, I then broke down the Drug Toxicity Monitoring Rules further into three sets of sub-rules.

The three sets of sub-rules started with the laboratory tests for drug toxicity (LFT and neutrophils). Three flowcharts for these sub-rules were illustrated (Figure 6.2-6.4). Figure 6.2 represented the sub-rule in the event of mild or moderate toxicity; Figure 6.3 represented the sub-rule in the event of severe toxicity; Figure 6.4 represented the sub-rule in the event of very severe toxicity.

The rule flowchart of the Rules for Changes in Dose/Agent I developed earlier featured combined sub-rules (Figure 5.6). I then separated the combine sub-rules and updated the flowchart. Figure 6.5 is the updated flowchart which illustrated the complete rule branches of the Rules for Changes in Dose/Agent.

The rectangle boxes from the flowcharts represented decisions or actions under a recognisable patient state; while the arrows indicated the sequence/flow of the clinical rules. The numbers on corners of the rectangle boxes labelled the sequence of the states within the rule set.

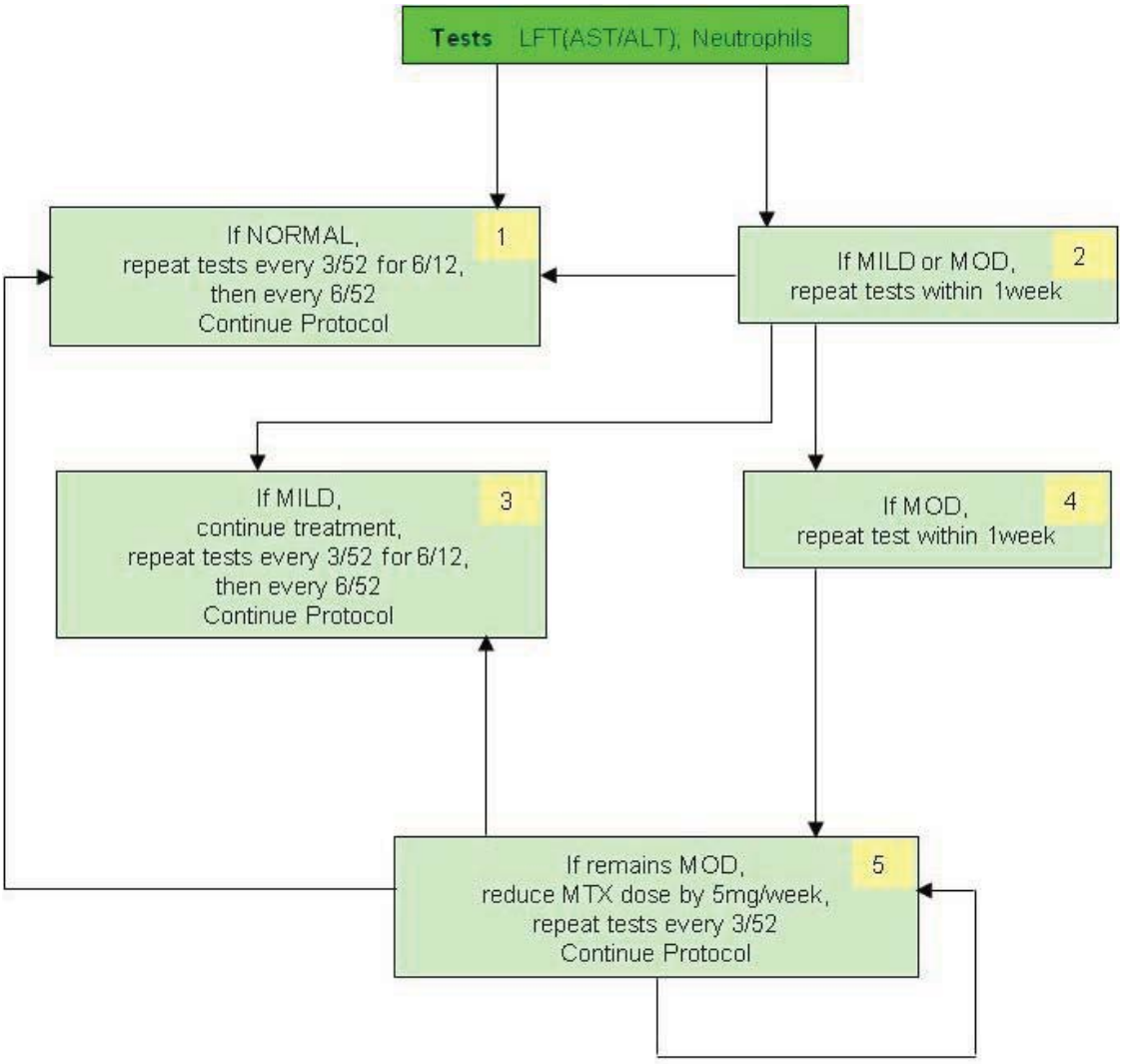


Figure 6.2 Rules for MTX monitoring in the event of mild or moderate toxicity

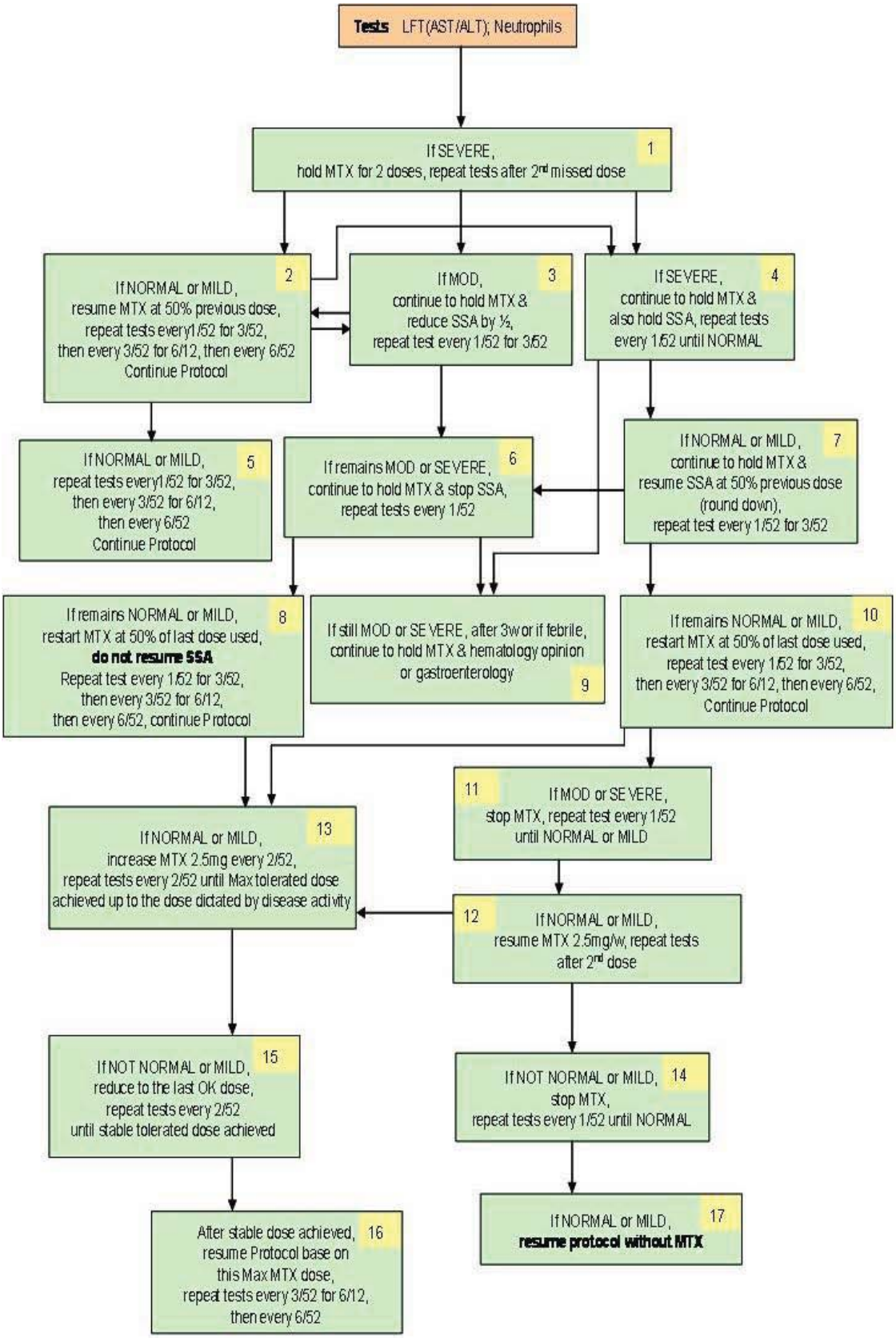


Figure 6.3 Rules for MTX monitoring in the event of severe toxicity

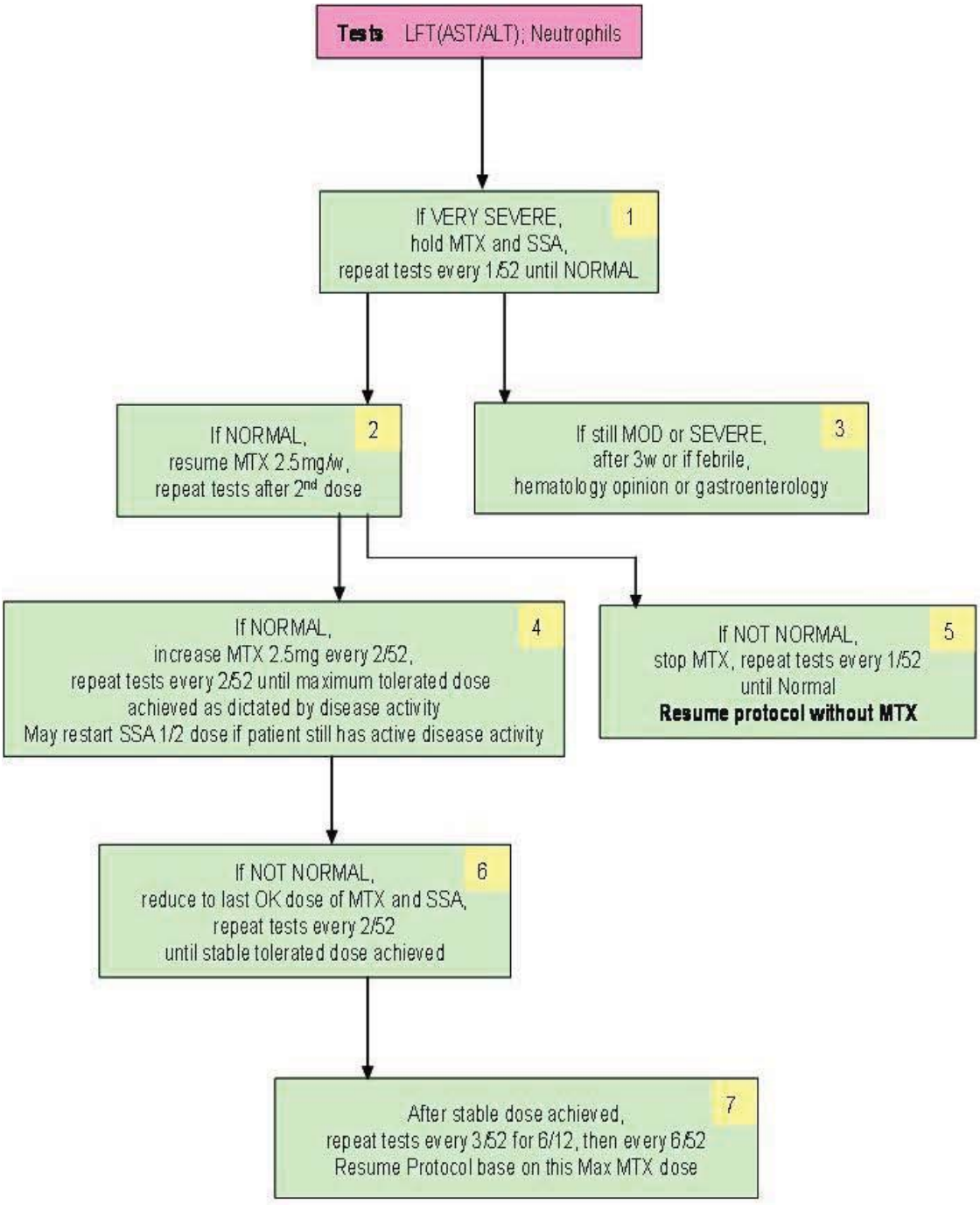


Figure 6.4 Rules for MTX monitoring in the event of very severe toxicity

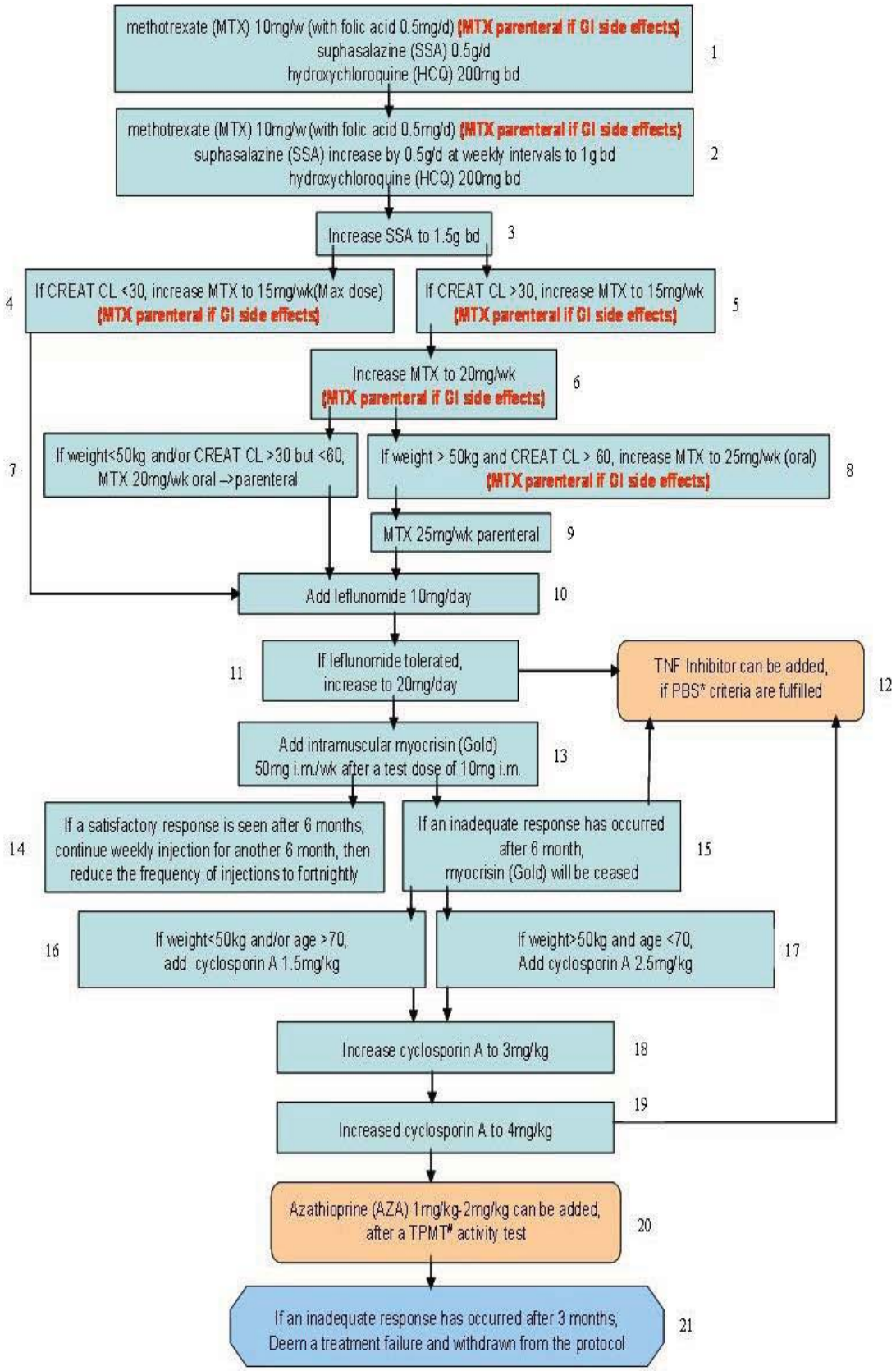


Figure 6.5 Rules for Changes in Dose and Agent

6.3 Exhaustive Search of State Transition Combinations in the Severe Toxicity sub-Rule

In order to manage a chronic disease such as RA, clinicians provide treatment to RA patients on a regular basis. Treatment adjustment is dependent on the decisions made and actions taken during a patient's previous and current visit. Clinicians can modify therapies over time depending on a patient's response to, and tolerance of the treatment.

Having created the flowchart for the severe toxicity sub-rule set, I illustrated the loops, time dependency and state transition in the event of severe drug toxicity. However, the transition loops brought the difficulties to work out the state transitions elementary. In order to demonstrate every potential state transition combination along the rule pathway exhaustively, I performed a "stress test" by walking through every possible rule branches manually; and then created a diagram demonstrating a complete set of state transition combinations (Figure 6.6). According to the thorough search, this diagram represented a complete set of state transition pathway within the severe toxicity sub-rule set.

Then I further analysed the diagram of the exhaustive state transition pathway. I identified a total of 19 alternative state transition combinations with 20 unique states in the severe toxicity rule set. A state was defined as 'unique' because the combination of its ancestor states and descendant states along the state transition pathway was exclusive. On the diagram, I used different colour code to represent each unique state if it had a special ancestor states and descendant states combination. However, if two states shared same descendant states but not the ancestor states, I applied same colour code but added an extra number to differentiate one from another.

Performing a "stress test" by walking through every possible rule branches manually gave an alternative way to demonstrate complexity and contingency of the RA management rules. It helped tremendously in understanding the state transition alternatives along the rule pathway, therefore establishing an algorithm to computerise the complex clinical rules.

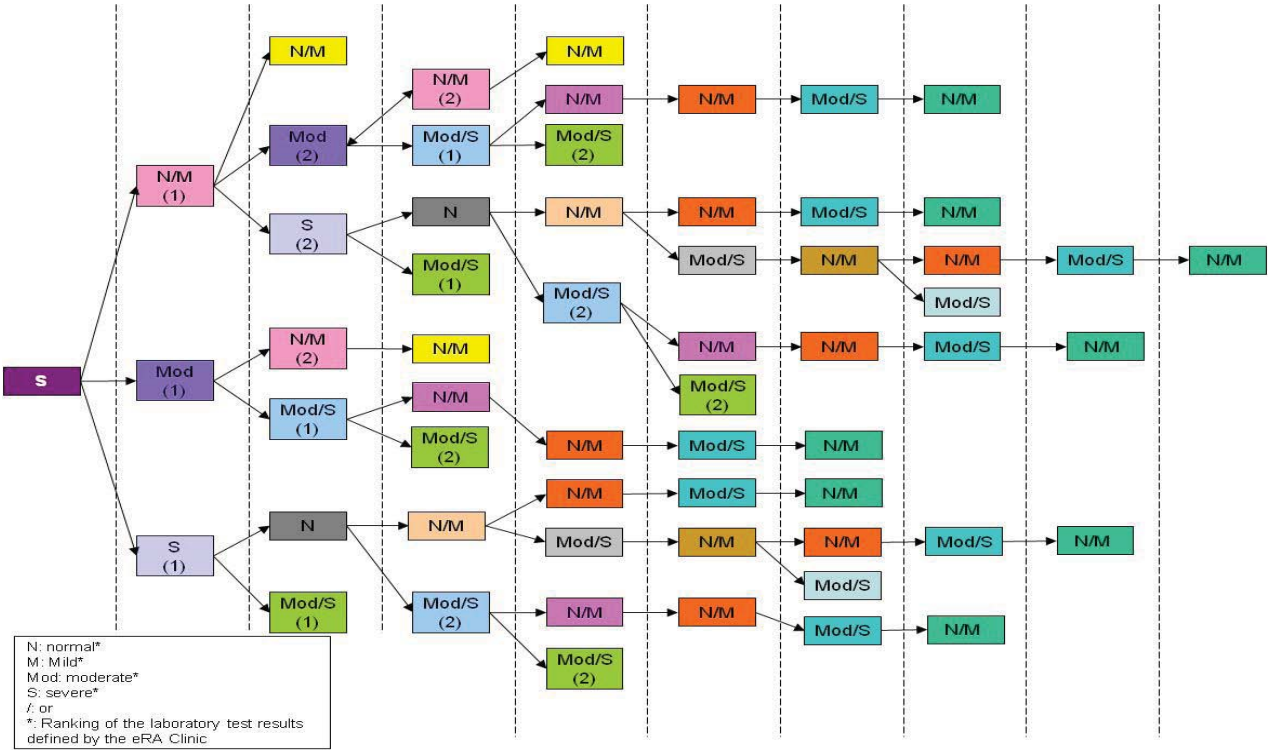


Figure 6.6 Exhaustive state flow combinations in the event of severe toxicity

6.4 Establishing Dynamic Model and Algorithm for the RA Management Rules

In order to translate the complex RA management rules into computer interpretable formats as a precursor to implementation utilising CDSS approach was to establish a dynamic model to represent the Drug Toxicity Monitoring Rules and the Rules for Changes in Dose/Agent. The dynamic model consisted of Decision Tables and Node Tables. A Decision Table contained static recommendations relating to specific patient clinical conditions (states). A node Table represents the dynamic relationships between these states.

According to the established rule flowcharts, two types of knowledge had been identified which were declarative knowledge and procedural knowledge. Declarative knowledge refers to specific clinical judgment such as scenarios and actions. For example, the first declarative knowledge within the severe toxicity rule set is 'if severe, hold MTX for 2 doses, repeat tests after 2nd missed dose'. Procedural knowledge includes sequences of the clinical judgments and transitions between the judgments. For example, the procedural knowledge relating to the first clinical judgment is either 'Normal/Mild' transition, or 'Moderate' transition, or staying at 'Severe' without a transition.

I transformed the flowcharts of the Drug Toxicity Monitoring Rules (mild or moderate toxicity rule set, severe toxicity rule set and very severe toxicity rule set) , and the Rules for Changes in Dose/Agent (Figure 6.2-6.5) into dynamic models (Figures 6.7-6.10) respectively. Each clinical scenario and associated actions within the boxes of the flowcharts was represented as a corresponding node of the dynamic model. Procedural knowledge was represented by a link with arrow connecting two nodes.

For each dynamic model, I further modelled procedural knowledge and declarative knowledge separately into a node table and a decision table. Firstly, I set up the node tables (Table 6.1, Table 6.3, Table 6.5, and Table 6.7) to specify the transitions and sequences of the clinical scenarios (procedural knowledge) for the dynamic models of

the Drug Toxicity Monitoring Rules (mild or moderate toxicity rule set, severe toxicity rule set and very severe toxicity rule set), and the Rules for Changes in Dose/Agent. Each node table included a complete set of nodes within its related dynamic model. All the corresponding descendant nodes were also listed. The 'Parent Node number' within the first column matched the numbers stated on its related dynamic model. Secondly, I created decision tables (Table 6.2, Table 6.4, Table 6.6 and Table 6.8) to sum up the declarative knowledge for the dynamic models. The decision tables illustrated the clinical scenarios and related actions for each node within the dynamic models.

Supplementing the dynamic models with the node tables and the decision tables captures knowledge encompassed within the RA management rules; CDSS application can be developed to access these decision tables. Both the node tables and the decision tables served as a knowledge base of the CDSS. Computer algorithms can be established according to the node tables for selecting required rules stored in the decision tables for execution.

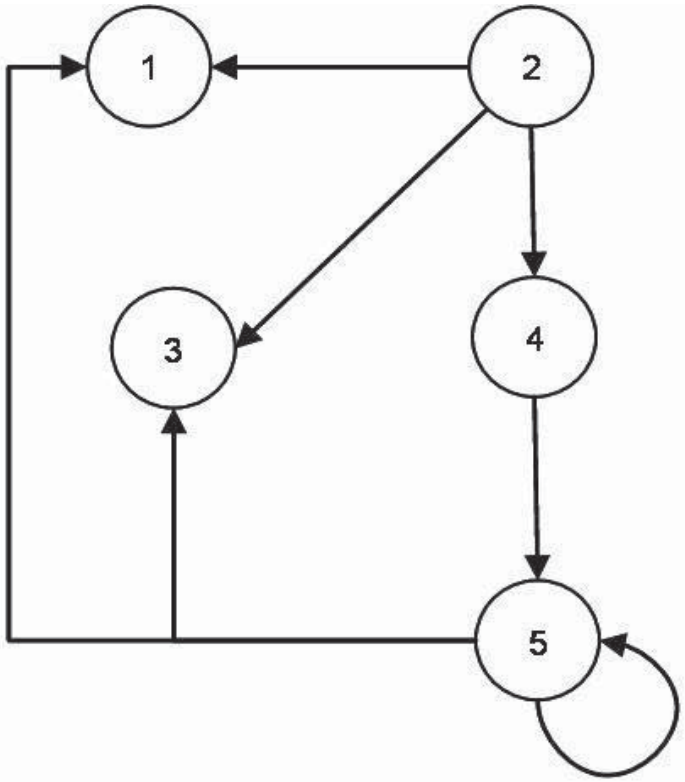


Figure 6.7 A dynamic model of the Drug Toxicity Monitoring Rules in the event of mild or moderate toxicity

Table 6.1 Node table of the Drug Toxicity Monitoring Rules
in the event of mild or moderate toxicity

Parent Node#	Child Node#		
	Normal	Mild	Moderate
1	-	-	-
2	1	3	4
3	-	-	-
4	-	-	5
5	1	3	5

Table 6.2 Decision table of the Drug Toxicity Monitoring Rules
in the event of mild or moderate toxicity

Node #	Scenarios	Action/Plan
1	If normal	Repeat tests every 3/52 for 6/12, then every 6/52, continue Protocol
2	If mild or moderate	Repeat tests within 1w
3	If mild	Continue treatment, repeat tests every 3/52 for 6/12, then every 6/52, continue Protocol
4	If moderate	Repeat test within 1w
5	If remains moderate	Reduce MTX dose by 5mg/w, repeat tests every 3/52, continue Protocol

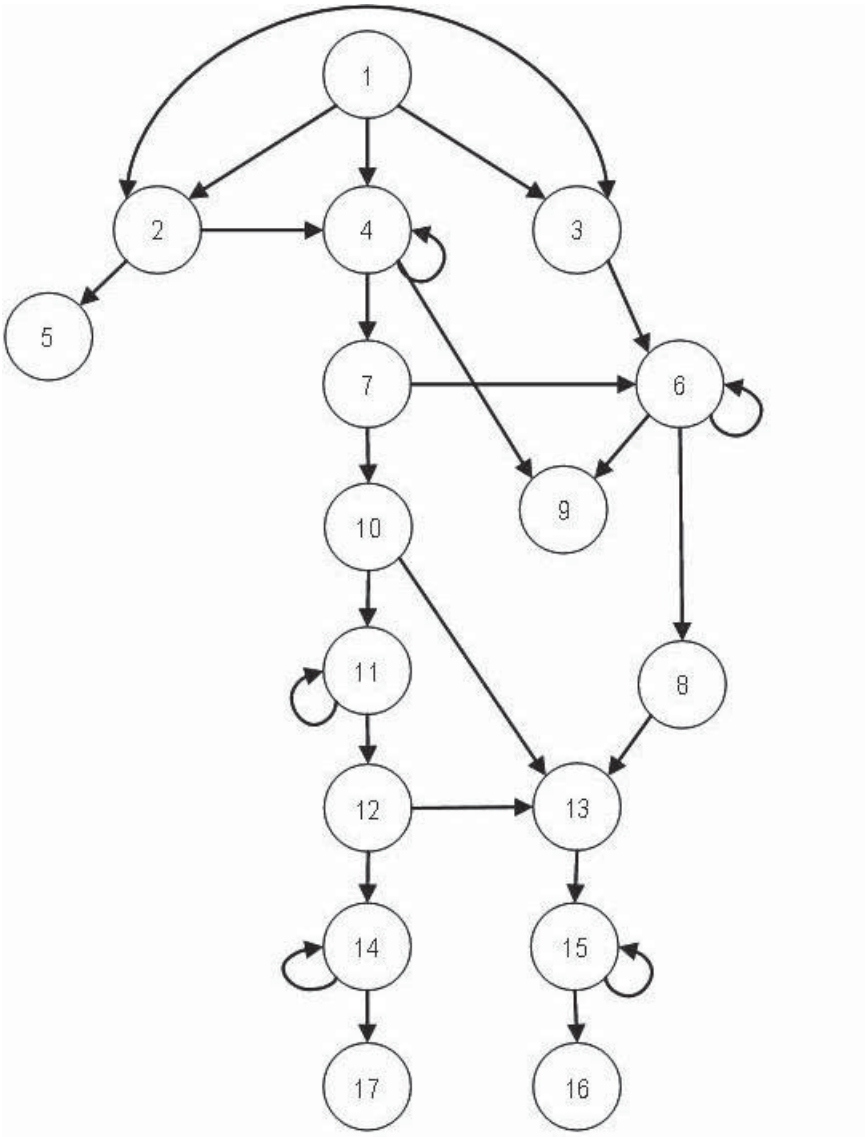


Figure 6.8 A dynamic model of the Drug Toxicity Monitoring Rules in the event of severe toxicity

Table 6.3 Node table of the Drug Toxicity Monitoring Rules
in the event of severe toxicity

Parent Node#	Child Node#		
	Normal/Mild	Moderate	Severe
1	2	3	4
2	5	3	4
3	2	6	6
4/1	7	4	4
4/2	7	9	9
5	-	-	-
6/1	8	6	6
6/2	8	9	9
7	10	6	6
8	13	-	-
9	-	-	-
10	13	11	11
11	12	11	11
12	13	14	14
13	13	15	15
14	17	14	14
15	16	15	15
16	-	-	-
17	-	-	-

Table 6.4 Decision table of the Drug Toxicity Monitoring Rules in the event of severe toxicity

Node #	Scenarios	Action/Plan
1	If severe	Hold MTX for 2 doses, repeat tests after 2nd missed dose
2	If normal/mild	Resume MTX at 50% previous dose, repeat tests every1/52 for 3/52, then every 3/52 for 6/12, then every 6/52, continue protocol
3	If moderate	Continue to hold MTX & reduce SSA by ½, repeat test every 1/52 for 3/52
4	If severe	Continue to hold MTX & also hold SSA, repeat tests every 1/52 until normal
5	If normal/mild	Repeat tests every1/52 for 3/52, then every 3/52 for 6/12, then every 6/52, continue protocol
6	If remains moderate/severe	Continue to hold MTX & stop SSA, repeat tests every 1/52
7	If normal/mild	Continue to hold MTX & resume SSA at 50% previous dose (round down), repeat test every 1/52 for 3/52
8	If remains normal/mild	Restart MTX at 50% of last dose used, do not resume SSA, repeat test every 1/52 for 3/52, then every 3/52 for 6/12, then every 6/52, continue protocol
9	If still moderate/severe	After 3w or if febrile, continue to hold MTX & haematology opinion or gastroenterology
10	If remains normal/mild	Restart MTX at 50% of last dose used, repeat test every 1/52 for 3/52, then every 3/52 for 6/12, then every 6/52, continue Protocol
11	If moderate/severe	Stop MTX, repeat test every 1/52 until normal/ mild
12	If normal/mild	Resume MTX 2.5mg/w, repeat tests after 2nd dose
13	If normal/mild	Increase 2.5mg every 2/52, repeat tests every 2/52 until maximum tolerated dose achieved up to dose dictated by

Node #	Scenarios	Action/Plan
		disease activity
14	If normal/mild	Stop MTX, repeat tests every 1/52 until normal
15	If normal/mild	Reduce to last OK dose, repeat tests every 2/52 until stable tolerated dose achieved
16		After stable dose achieved, resume protocol based on this as maximum MTX dose, repeat tests every 3/52 for 6/12, then every 6/52
17	If normal/mild	Resume protocol without MTX

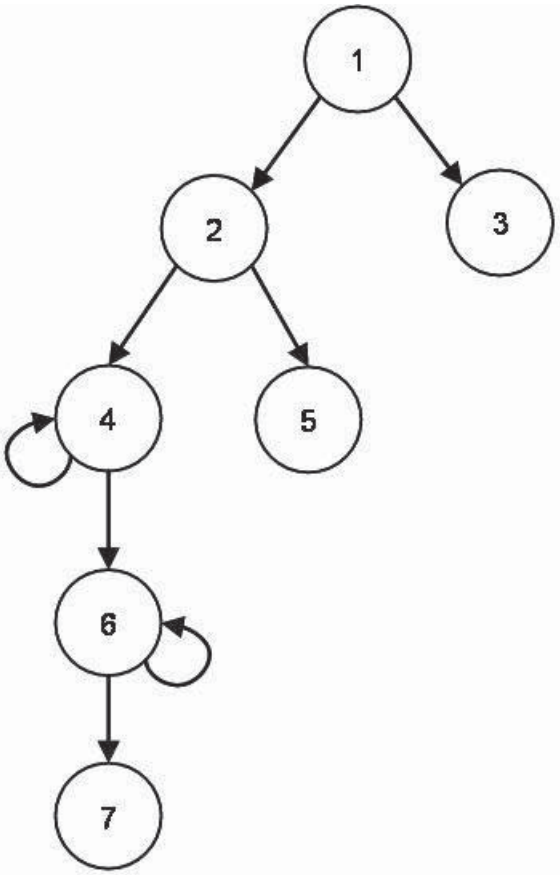


Figure 6.9 A dynamic model of the Drug Toxicity Monitoring Rules in the event of very severe toxicity

Table 6.5 Node table of the Drug Toxicity Monitoring Rules
in the event of very severe toxicity

Parent Node#	Child Node#		
	Normal/Mild	Moderate	Severe
1	3	2	2
2	4	5	5
3			
4	4	6	6
5	-	-	-
6	7	6	6
7	-	-	-

Table 6.6 Decision table of the Drug Toxicity Monitoring Rules
in the event very severe toxicity

Node #	**Scenarios**	**Action/Plan**
1	If very severe	Hold MTX and SSA, repeat tests every week until normal
2	If normal	Resume MTX 2.5mg/w, repeat tests after 2nd dose
3	If still moderate/severe	After 3w or if febrile, haematology opinion or gastroenterology
4	If normal	Increase 2.5mg every 2/52, repeat tests every 2/52 until maximum tolerated dose achieved as dictated by disease activity, may restart SSA 1/2 dose if patient still has active disease activity
5	If not normal	Stop MTX, repeat tests every 1/52 until normal, resume protocol without MTX
6	If not normal	Reduce to last OK dose of MTX and SSA, repeat tests every 2/52, until stable tolerated dose achieved
7		After stable dose achieved, repeat tests every 3/52 for 6/12, then every 6/52, resume protocol based on this as maximum MTX dose

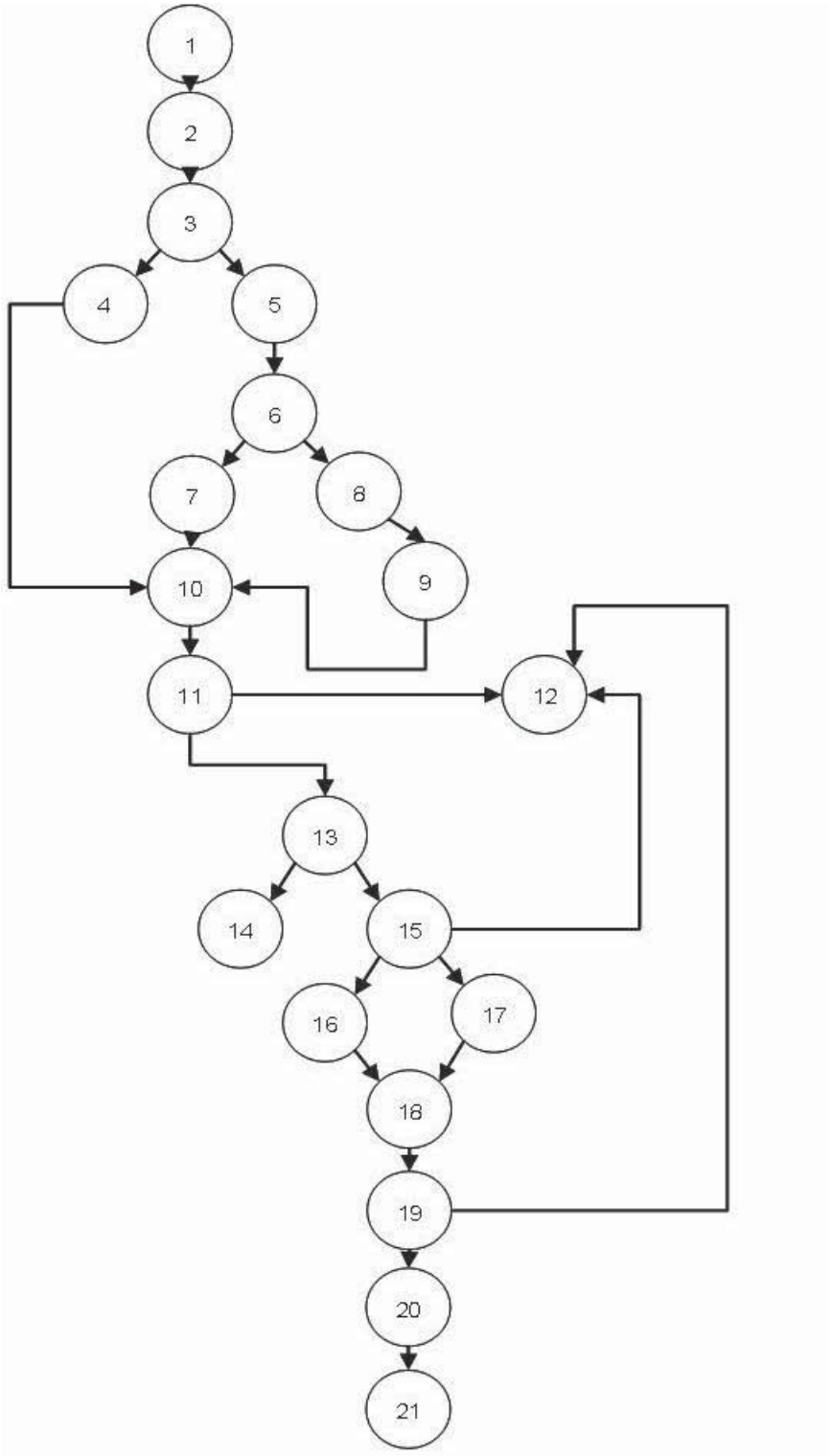


Figure 6.10 A dynamic model of the Rules for Changes in Dose/Agent

Table 6.7 Node table of the Rules for Changes in Dose/Agent

Parent Node#	Child Node#			
	Unconditional	Condition	Satisfied	Not satisfied
1	2	-		
2	3	-		
3	-	If CREAT CL<30 ml/min	4	5
4	10	-		
5	6	-		
6	-	If weight <50 and/or CREAT CL >30 but <60 ml/min	7	8
7	10	-		
8	9			
9	10			
10	11			
11	-	PBS criteria fulfilled	12	13
12	-	-		
13	-	If satisfactory response after 6 month	14	15
14	-	-		
15	-	If weight <50 kg and/or age >70 years	16	17
16	18	-		
17	18	-		
18	19	-		
19	-	PBS criteria fulfilled	12	20
20	21	-		
21	-	-		

Table 6.8 Decision table of the Rules for Changes in Dose/Agent

Node #	Scenarios	Action/Plan
1		MTX 10mg/w (with folic acid 0.5mg/d) (MTX parenteral if GI side effects), SSA 0.5g/d, HCQ 200mg bd
2		MTX 10mg/w (with folic acid 0.5mg/d) (MTX parenteral if GI side effects), SSA increase by 0.5g/d at weekly intervals to 1g bd, HCQ 200mg bd
3		Increase SSA to 1.5g bd
4	If CREAT CL <30 ml/min	Increase MTX to 15mg/wk (Max dose) (MTX parenteral if GI side effects)
5	If CREAT CL >30 ml/min	Increase MTX to 15mg/wk (MTX parenteral if GI side effects)
6		Increase MTX to 20mg/wk (MTX parenteral if GI side effects)
7	If weight<50kg and/or CREAT CL >30 but <60 ml/min	MTX 20mg/wk oral –>parenteral
8	If weight > 50kg and CREAT CL > 60 ml/min	Increase MTX to 25mg/wk (oral) (MTX parenteral if GI side effects)
9		MTX 25mg/wk parenteral
10		Add leflunomide 10mg/day
11		If leflunomide tolerated increase to 20mg/day
12		TNF Inhibitor can be added, if PBS criteria are fulfilled
13		Add intramuscular Gold 50mg i.m./wk after a test dose of 10mg i.m
14		If a satisfactory response is seen after 6 months,

Node #	Scenarios	Action/Plan
		continue weekly injection for another 6 month, then reduce the frequency of injections to fortnightly
15		If an inadequate response has occurred after 6 month, Gold will be ceased
16		If weight<50kg and/or age >70, add cyclosporine A 1.5mg/kg
17		If weight>50kg and age <70, add cyclosporine A 2.5mg/kg
18		Neoral will be increased to 3mg/kg
19		Neoral will be increased to 4mg/kg
20		AZA 1mg/kg-2mg/kg can be added, after a TPMT activity test
21		If an inadequate response has occurred after 3 months, deem a treatment failure and withdraw from the protocol

6.5 Drug Toxicity Prediction Model

The risk of developing drug toxicity varies between individuals and may hinder the achievement of optimal doses of DMARDs. Yet, the Dose Modification Protocol of the eRA clinic provides standard treatment recommendations that were not designed to accommodate out-of-range laboratory results or other factors that can contribute to an individual patient's risk for developing significant toxic effects from agents within the combination therapy regimen. It has therefore been incumbent on clinicians to utilise additional knowledge to estimate the risk of drug toxic effects developing in individual patients and to adjust treatment accordingly. To monitor risk, clinicians examine factors such as prevailing clinical symptoms, out-of-range laboratory results and the patient's co-morbidities and past medical history. Failure to develop a set of rules for responding to out-of-range laboratory results was a source of avoidable practice variability that came to light during the eRA-CDSS project.

The eRA clinic has been aiming to apply routine surveillance for drug toxicity and nuisance side effects associated with the Triple Therapy or its components, including effects on the lungs, blood cells, liver, gastrointestinal tract and retina (refer to chapter 5.2.3). However in order to systematically integrate these drug toxicity risks into the clinical decision-making process and to complement the eRA clinical guidelines, drug toxicity prediction models needed to be established to tailor guidelines better to individual patient management. In this undertaking, I use Bayes' Theorem and Bayes Net to explain the establishment of the drug toxicity prediction model.

6.5.1 Bayes' Theorem

In many situations, estimates of the probability of outcome events can be revised as further information becomes available. During decision-making of RA treatment for a given patient under a given drug regimen, the clinician can estimate the probability of a patient developing drug-related toxic effects. However, should the clinician notice a patient has an elevated serum liver enzyme result, the probability of having developing significant drug-related liver toxicity will increase. This is the conditional probability

of drug toxic effects under the drug regimen given that the patient has an elevated liver enzyme result.

P(A | B) denotes the probability that event A will occur given that event B has occurred already. Conditional probabilities can also be denoted as causal relationship, which is P(Effect | Cause).

Bayes' Theorem provides a method of manipulating conditional probabilities. It allows new information to be used to update the conditional probability of an event [4]. These appear frequently when making medical diagnoses. It has proven to be very useful, and is used in programming to help diagnose diseases**.**

P(Effect | Cause)=(P(Cause | Effect)*P(Effect))/P(Cause)

Bayes' Theorem can be used for reversing a conditional probability and combining evidence for decision-making.

6.5.2 Bayes Net

A Bayes Net is a model that reflects the states of some part of a world, and it describes how those states are related by probabilities. Bayes Nets are directed acyclic graphs where each node represents a random variable. Bayes Nets naturally represent causal chains, that is, the links represent cause-effect relationships between parent and child nodes. Each node corresponds to some condition of the patient. The influences are measured by conditional probabilities. Figure 6.11 is a graphical representation of a sample casual independence model using Bayes Nets.

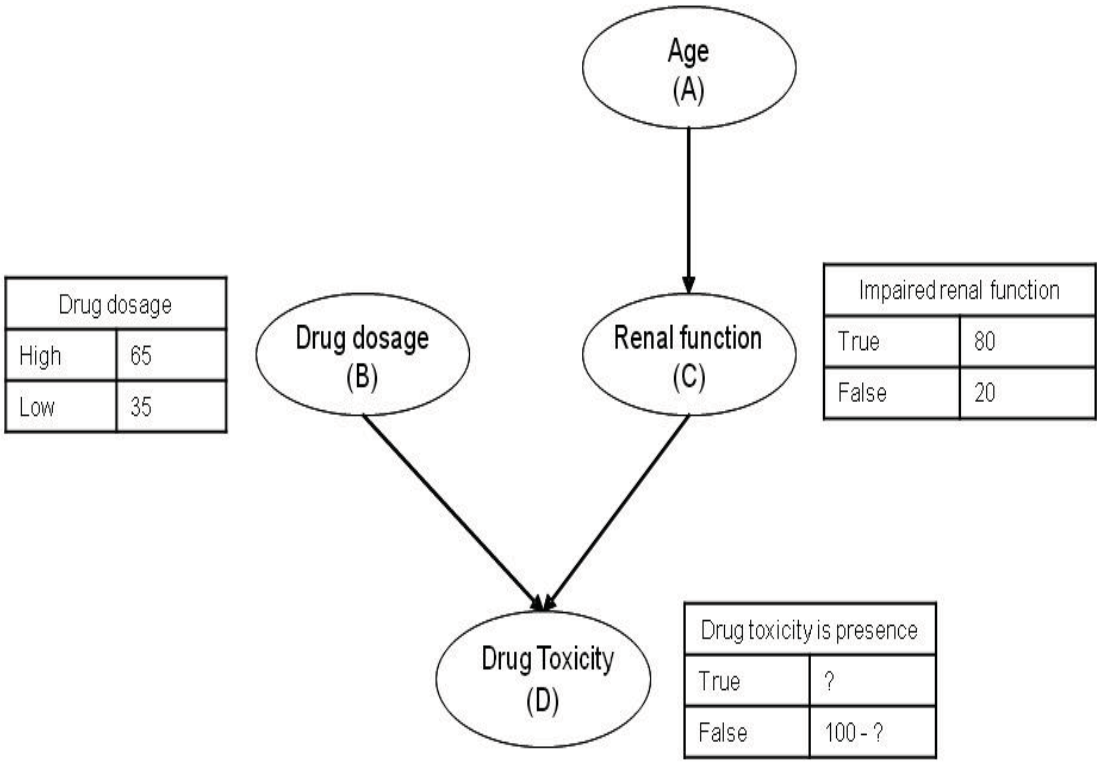


Figure 6.11 A sample casual model of Bayes Nets

Because Bayes Nets describe how these parent-child nodes are related by probabilities; they can be used to make predictions in the context of clinical decision-making. Bayes Nets can project the most likely outcomes by supplying the best available evidence. Bayes Nets express the probable conditional independence, allowing a compact representation of the joint distribution. They only recount nodes that are probabilistically related by some sort of causal dependency, resulting in an enormous saving of computation.

$$P(D \mid A, B, C) = P(D \mid B, C)$$

From the illustrated sample casual model (Figure 6.11), in order to generate the probability of the drug toxicity presence, we need to know the information regarding to:

1. the probability of drug toxicity presence under the condition of high drug dosage was true and impaired the renal function was true

2. the probability of drug toxicity presence under the condition of high drug dosage was false and impaired the renal function was true
3. the probability of drug toxicity presence under the condition of high drug dosage was true and impaired the renal function was false
4. the probability of drug toxicity presence under the condition of high drug dosage was false and impaired the renal function was false

In other words, we needed to know the probability values of the data A to D within the Table 6.9. Since the Bayes Nets model uses these values to formulate prediction rules, and then the model can compile the probability we were looking for, that was the probability of drug toxicity presence (refer to Figure 6.11).

When the Bayes Nets model is implemented into a CDSS, the CDSS can further help to collect utility data from clinicians before implementing the decision tree model (refer to chapter 2.8.2).

Table 6.9 Drug toxicity causal probability table

Causal dependency nodes		Drug toxicity (probability %)	
High drug dosage	Impaired renal function	Present	Absent
True	True	A	100-A
True	False	B	100-B
False	True	C	100-C
False	False	D	100-D

6.5.3 Establish Methotrexate Toxicity Prediction Model

Prior to establishing a drug toxicity prediction model for MTX, I performed a comprehensive review of the literature on risk factors of MTX toxicity in RA (refer to chapter 2.7.4), As a result of this review; I identified a broad range of evidence-based toxicity risk factors for developing MTX toxicity. I categorised the risk factors into five major categories (refer to chapter 5.2.1); they are (1) common risk factors for MTX toxicity, (2) MTX pulmonary toxicity risk factors, (3) MTX hepatic toxicity risk factors, (4) MTX haematological toxicity risk factors, and (5) MTX gastrointestinal toxicity risk factors. In addition, I classified the major MTX toxic effects into four groups (refer to chapter 5.2.2); they are (1) MTX pulmonary toxic effects, (2) MTX hepatic toxic effects, (3) MTX haematological toxic effects, and (4) MTX gastrointestinal toxic effects.

I employed a Bayes Net causal model to set up the MTX toxicity prediction model. I applied the categorised risk factors as evidence nodes on the causal chains. The corresponding MTX toxicity (e.g. MTX hepatotoxicity), was represented as a query node. The model demonstrated cause-effect relationships between the risk factors and the toxicity consequences. In addition to the risk factors, the drug toxicity prediction model included secondary evidence nodes (MTX toxic effects) on the causal chains, such as relevant out-of-range laboratory results and relevant clinical symptoms. These secondary evidence nodes are the consequences of the query node.

The establishment of the drug toxicity prediction model applied Probability Theory and Bayes Theorem. Each consequence node corresponds to some condition of the risk factor nodes. The influences are measured by conditional probabilities. Therefore, by supplying patient risk factors, relevant laboratory test results and drug toxicity related symptoms, this model can predict the probability of developing MTX toxicity in an individual patient. However, for every causal relationship on the causal chain, the causal probability table must be available for the model to generate the query probability.

In order to maximise expected utility while making decision under uncertainty, the establishment of the drug toxicity prediction models can provide assistance to clinicians in estimating the probability of developing drug toxicity. The estimated probability of developing drug toxicity can help clinicians make treatment decisions tailored to the specific situation of individual patients.

The MTX toxicity prediction model can be computerised and the probability of developing drug toxicity can be predicted and presented to the clinician. Incorporating this automated evidence-based MTX toxicity prediction model into the decision-making process promises to reduce the incidence of clinically significant MTX toxicity by adjusting a therapy before toxic effects occur. Alternatively, the computed risk assessment may prevent clinicians over-reacting and withdrawing treatment when not warranted by the extent of risk. The MTX toxicity prediction model may thereby help maintain patients on MTX on longer on effective doses thereby realising greater therapeutic benefits.

Figures 6.12-15 shows the Bayes Nets models for MTX Hepatotoxicity Prediction, MTX Haematological Toxicity Prediction, MTX Pulmonary Toxicity Prediction and MTX Gastrointestinal Toxicity Prediction respectively. These models incorporated the evidence-based MTX toxicity risk factors and the MTX toxic effects which I summarised in chapter 5.2.

Theoretically, the drug toxicity model can estimate probabilities for the occurrence of toxicity provided a completed causal probability table is available. However, the literature review failed to pin down probability data quantifies the rate of MTX toxicity occurrence in the presence of realised risk factors, or the rate of MTX toxic effect occurrence in the presence of MTX toxicity. As such, these conditional probabilities along causal chains of the model were not available to generate the probability of the query node. While these deficiencies are barriers to model implementation, they have identified questions for research that could lead to better management.

I used the MTX pulmonary toxicity prediction model (refer to Figure 6.14) as an example to give more detailed explanation. The query node of this model was MTX pulmonary toxicity. In order to generate the probability for presence of MTX pulmonary toxicity, the model needs three causal probability tables (Table 6.10 – 6.12) to be filled with the required probability data. However the required conditional probabilities data A to H were not available from the literature. These data quantifies the rate of MTX pulmonary toxicity occurrence in the presence of smoking or pre-existent pulmonary diseases, or the rate of toxicity related symptoms and abnormal laboratory test results occurrences in the presence of MTX pulmonary toxicity. As such, the model cannot be implemented to generate the query probability.

The study failed to implement the MTX toxicity prediction models due to lack of availability of conditional probabilities in the literature for estimating risk for MTX toxicity. Consequently, the study cannot utilise computerised MTX pulmonary toxicity prediction model for further collecting utility data, therefore the decision tree model was unable to be implemented during the study. Nevertheless, the establishment of the architecture for the model had set the framework for future continuous model development and implementation.

Table 6.10 MTX pulmonary toxicity causal probability table I

Causal dependency nodes		Pulmonary toxicity (probability %)	
Smoking	Pre-existent pulmonary disease	Present	Absent
True	True	A	100-A
True	False	B	100-B
False	True	C	100-C
False	False	D	100-D

Table 6.11 MTX pulmonary toxicity causal probability table II

Causal dependency nodes	Related Symptom (probability %)	
Pulmonary toxicity	Present	Absent
True	E	100-E
False	F	100-F

Table 6.12 MTX pulmonary toxicity causal probability table III

Causal dependency nodes	Related Lab result (probability %)	
Pulmonary toxicity	Normal	Abnormal
True	G	100-G
False	H	100-H

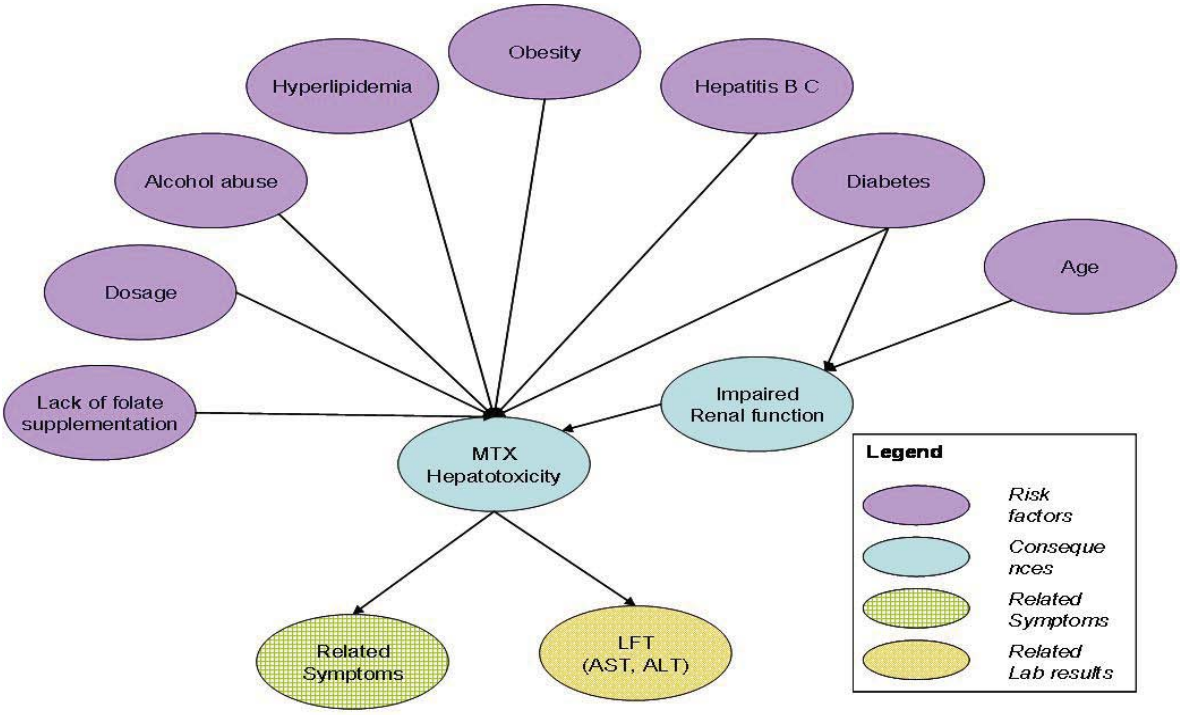


Figure 6.12 The MTX Hepatotoxicity Prediction Model

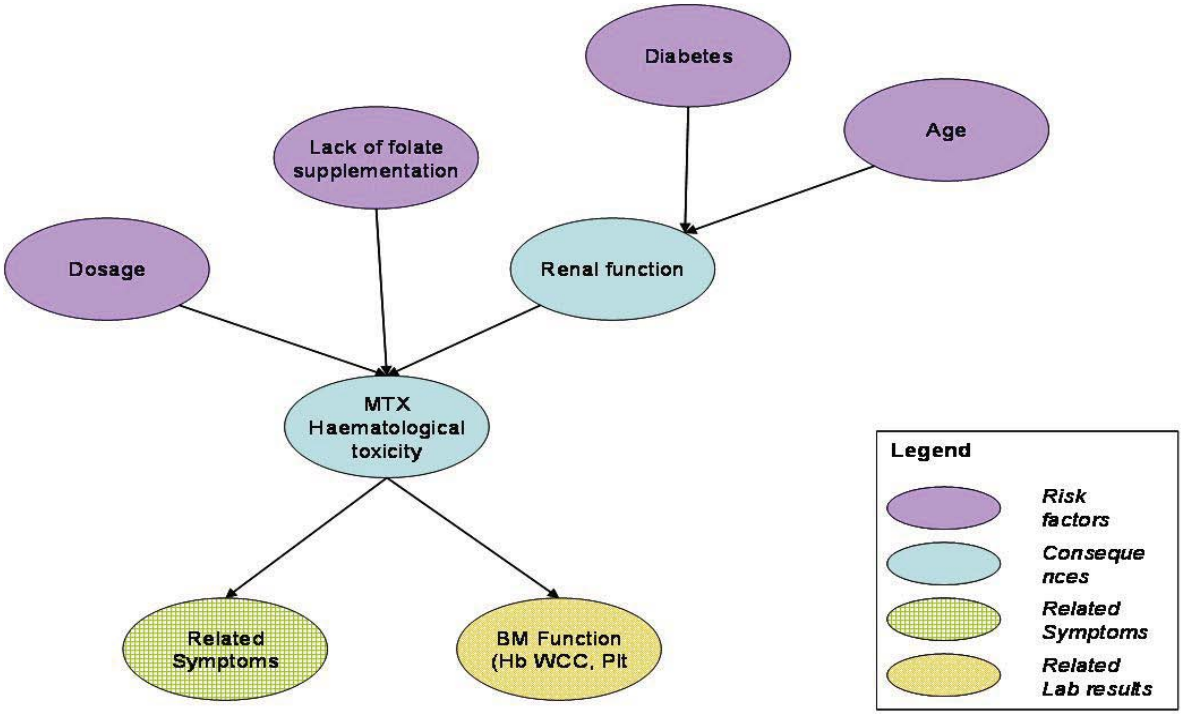


Figure 6.13 The MTX Haematological Toxicity Prediction Model

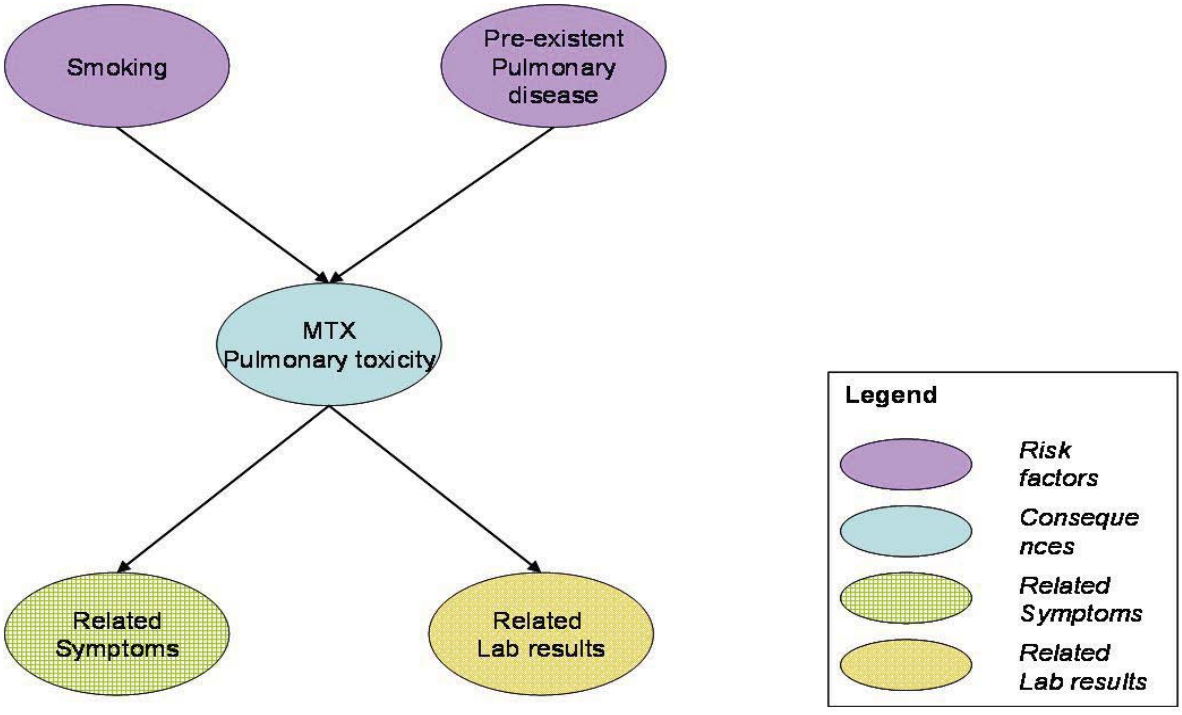


Figure 6.14 The MTX Pulmonary Toxicity Prediction Model

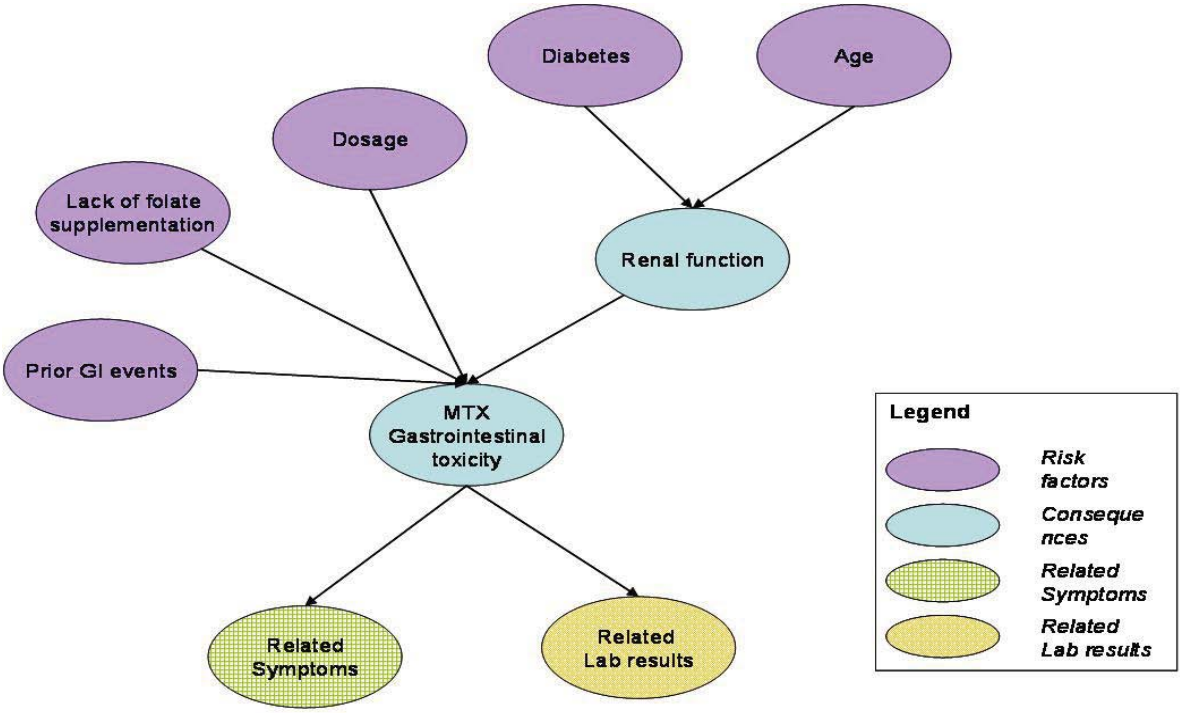


Figure 6.15 The MTX Gastrointestinal Toxicity Prediction Model

6.6 Integrate the RA Management Rules into the eRA Practice

For efficiency, decision support must be seamlessly integrated into clinicians' decision-making procedures. Therefore, clinical guidelines and supporting evidence that are used by clinicians in their decision-making need to be delivered to each decision-making point.

Base on the clinical consultants I observed, I performed an analysis of when clinicians apply clinical guidelines and expertise and of the procedures for applying clinical guidelines and expertise. With an understanding of how the clinicians integrate the clinical guidelines and their expertise into their practice, I mapped the RA management rules against the appropriate decision-making points.

6.6.1 Map the RA Management Rules into the eRA Patient Assessment Process

In the eRA clinic, previous analysis of the patient assessment process showed that the clinical decision-making integrates the eRA guidelines and additional knowledge to estimate drug toxicity risk. The latter and contingent responses were not systematised and were therefore a source of avoidable practice variability.

After the eRA clinic established the comprehensive RA management rules, the clinicians applied two sets of rules during the decision-making process in order to adjust a treatment. They were the Dose Modification Protocol and the Rules for Changes in Dose/Agent. Drug Toxicity Monitoring Rules were developed in this project to complement former rules including the Triple Therapy and the Dose Modification Protocol.

During the RA patient assessment process, if a patient's laboratory results are out-of-range, clinicians can now apply the Drug Toxicity Monitoring Rules to tailor a drug regimen and dosage recommendation to accommodate risks for clinically significant toxicity displayed by the patient. If the patient has normal laboratory results, clinicians apply the Dose Modification Protocol. If a change in dosage is required by the protocol,

the clinicians apply the Rules for Changes in Dose/Agent to gain a drug regimen and dosage recommendation. If out-of-range blood results occur, the Drug Toxicity Monitoring Rules take priority. The drug toxicity prediction model can be applied to generate the probability of drug toxicity developing in the individual patient and may be used to revise guidelines to adjust these risks or intensify adverse effects monitoring.

With clinicians combining the guideline recommendations and the drug toxicity prediction outcome, management may be refined. I have mapped the eRA clinical guidelines and the drug toxicity prediction model into the patient assessment process (Figure 6.16).

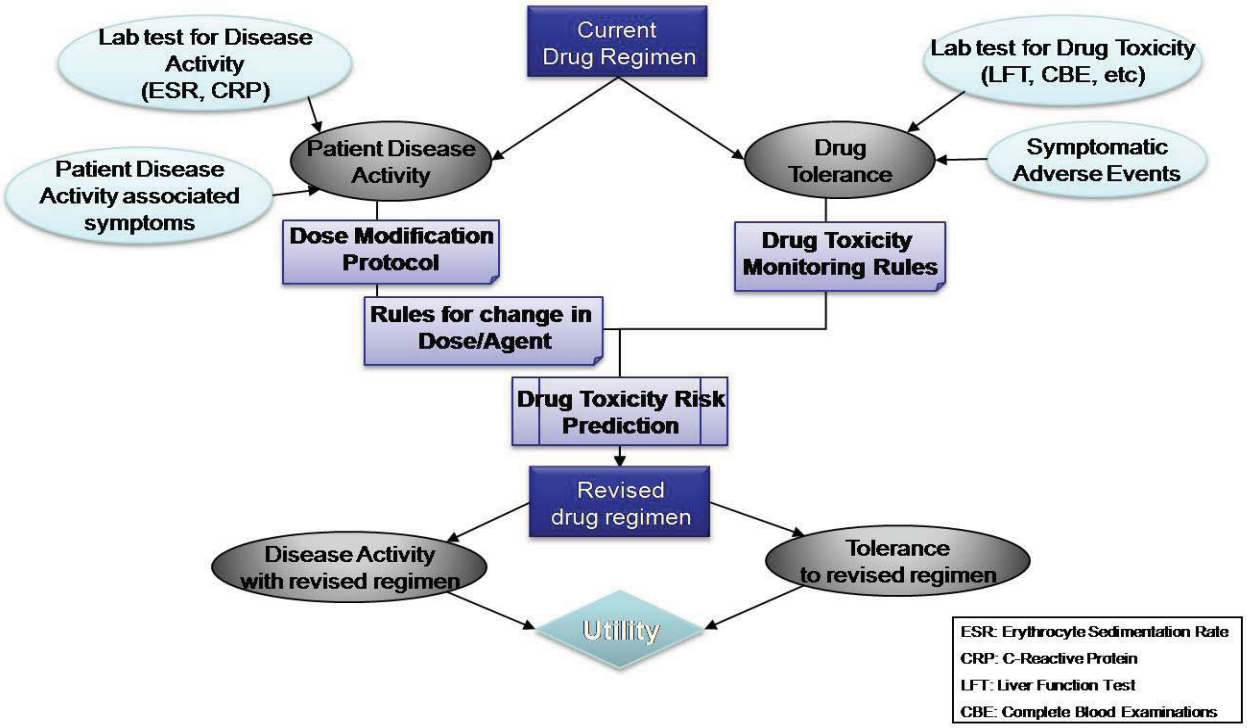


Figure 6.16 The RA management rules and toxicity prediction model are integrated into the patient assessment process

6.6.2 Analyse the Decision-Making Procedure in the eRA Clinic

To deliver timely clinical decision support, CDSS should understand clinical decision-making procedures. In the eRA clinic, clinicians applied the clinical rules, protocols and the newly established RA management rules in a particular order to reach a final decision on adjusting a treatment.

I analysed the decision-making process of the eRA clinic. Based on an understanding of the type of clinical knowledge/evidence and when the clinical knowledge/evidence should be incorporated by clinicians into the decision-making process, I established a graphical representation of the decision-making porcedure of assessing an RA patient in the eRA clinic. It maps the eRA Dose Modification Protocol, RA management Rules, and the drug toxicity prediction to the decision-making points.

Figure 6.17 illustrated the sequential process of clinical decision-making in the eRA clinic. The process started from retrieving patient clinical data and laboratory data. The diamond boxes stood for decision-making points. The rounded rectangle boxes represented predicting risk of developing drug toxicity. The grey rectangle boxes denoted the final decisions on patient treatment.

I also translated this sequential process into an UML Activity Diagram (Figure 6.18). The UML diagram can be easily understood by software developers. By establishing the decision-making procedure, a foundation is provided for the application design and implementation. Based on this procedure, computer algorithms can be set up and patient data can be determined for CDSS implementation.

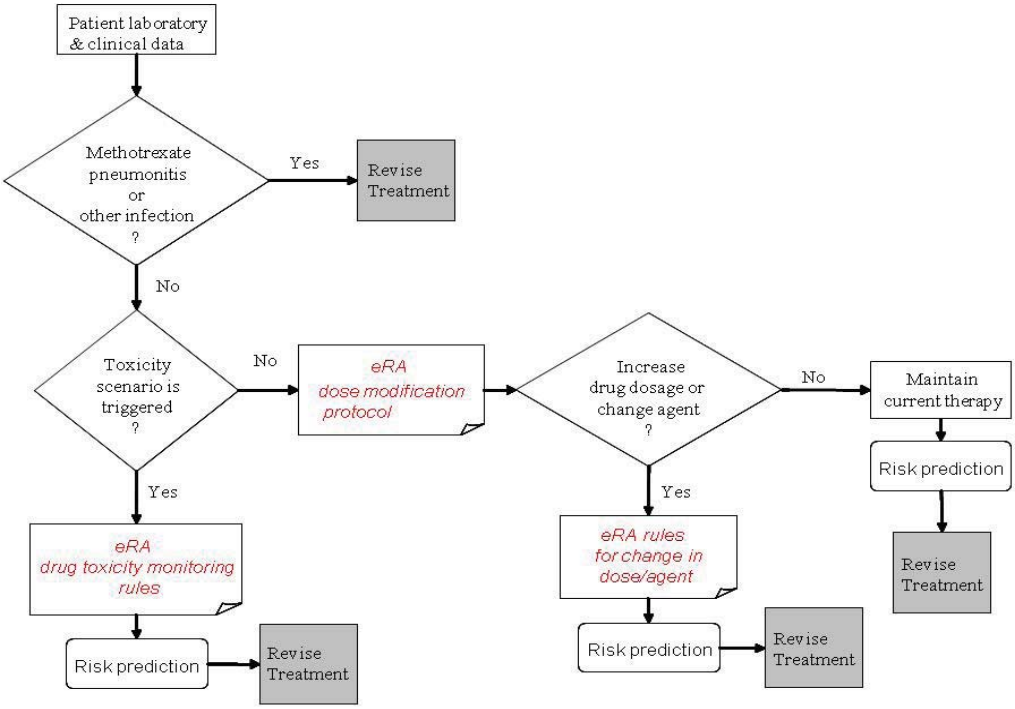


Figure 6.17 The eRA decision-making procedure

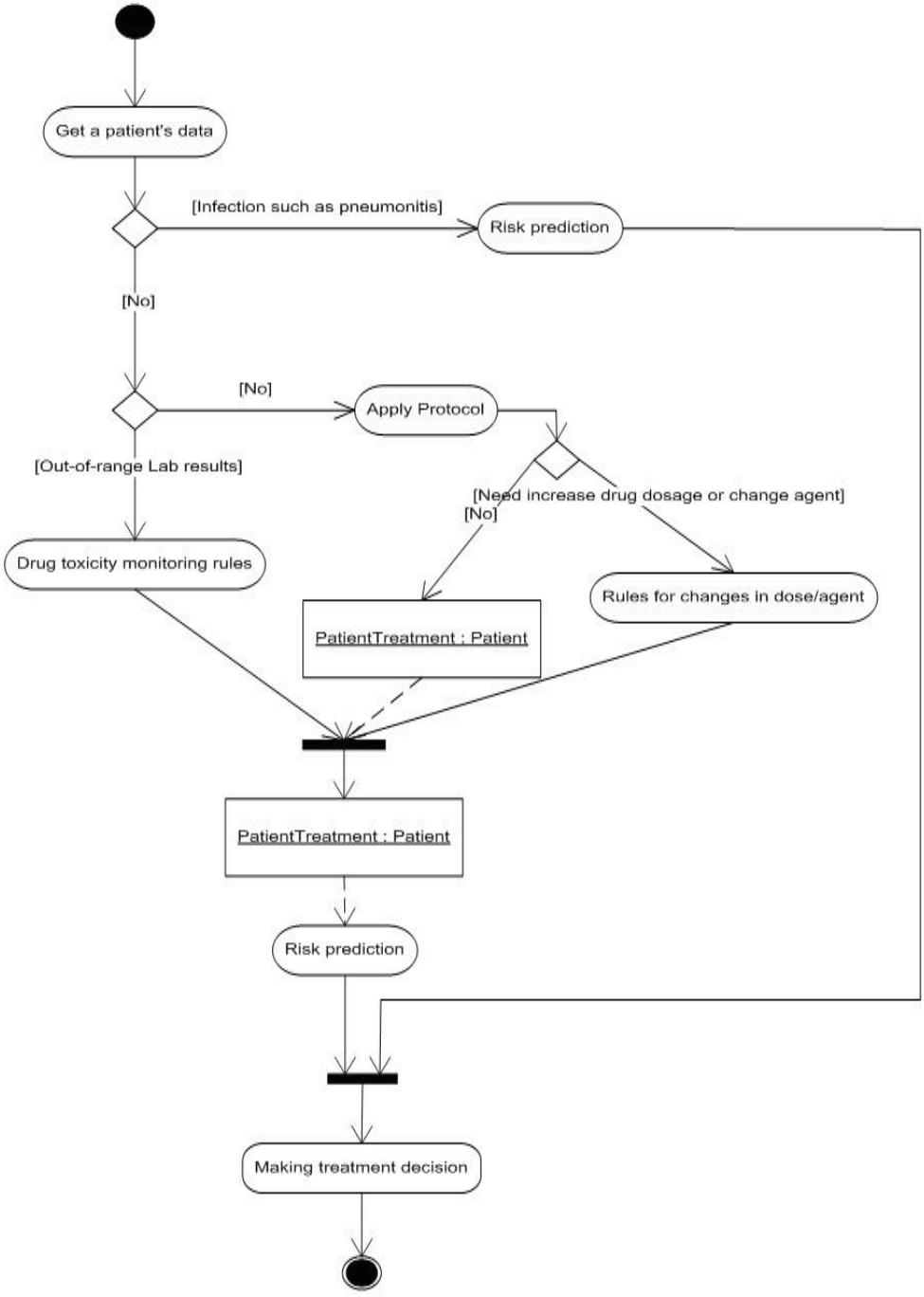


Figure 6.18 The UML Activity Diagram of the eRA decision-making procedure

7 The eRA-CDSS

In managing RA, best practice requires the adjustment of medication dosages and the substitution of medications according to a patient's response and tolerance. These factors demand close monitoring of disease activity and of certain blood investigations that are used to monitor safety, as well as consistent considered responses to abnormal findings.

In the eRA clinic, practising EBM requires clinicians to comply with CPGs while making clinical decisions. However, Drug Toxicity Monitoring Rules and Rules for Changes in Dose/Agent are complex. It is difficult for clinicians to manually apply such complex rules during busy consultations. The complexity of the eRA guidelines contrasts with that of usual therapeutic guidelines which are designed as general statements intended to guide practice for populations of patients, with the expectation that individual clinicians will apply considerable discretion in their application in practice according to the many contingent circumstances about which the guidelines are silent. The eRA guidelines differ in attempting to anticipate contingent events in order to provide more specific guidance that reduces practice variability. The eRA guidelines are thus more prescriptive than usual guidelines and thus substantially more complex. This complexity is problematic for administration of paper-based guidelines and more suited to delivery in a point of care using CDSSs.

In order to (1) facilitate the compliance of complex eRA guidelines and reinforce the integration of extra knowledge into decision-making processes in a systematic fashion, and (2) assist clinicians in making better clinic decisions when adjusting therapy according to treatment response and drug tolerance, the study developed a CDSS specific to the eRA clinic (eRA-CDSS), in which a relatively orderly approach to managing RA had already been established.

7.1 Rule-based Expert System

A rule-based expert system is a knowledge-based program that provides 'expert quality' solutions to problems in a specific domain. Its knowledge is extracted from human experts in the domain and it attempts to emulate their methodology and performance [171]. The eRA-CDSS is such a rule-based expert system. Having adopted Knowledge Acquisition, the eRA clinic established the comprehensive RA management rules which form a knowledge base. Automation of highly complex clinical rules is the core functionality of the eRA-CDSS. Figure 7.1 illustrates the basic architecture of an expert system.

1. Knowledge Base

   Knowledge base contains the domain knowledge used for problem solving. Knowledge is represented as rules having the IF (condition) THEN (action) structure.
2. Database

   Database includes facts used to match against the IF part of the rules stored in the knowledge base.
3. Inference Engine

   Inference Engine provides a solution by reasoning, linking the rules with the facts.
4. Explanation Facility

   Explanation Facility explains how a particular conclusion is reached and why a specific fact is needed.
5. User Interface

   User Interface enables communication between a user seeking a solution to a problem, and an expert system.
6. Developer Interface

   Developer interface enables a knowledge-base editor to insert and modify rules. It has debugging capabilities in order to trace and examine the rules and data. An input/output facility such as runtime Knowledge Acquisition enables the running expert system to ask for required information whenever this information is not available in the database.

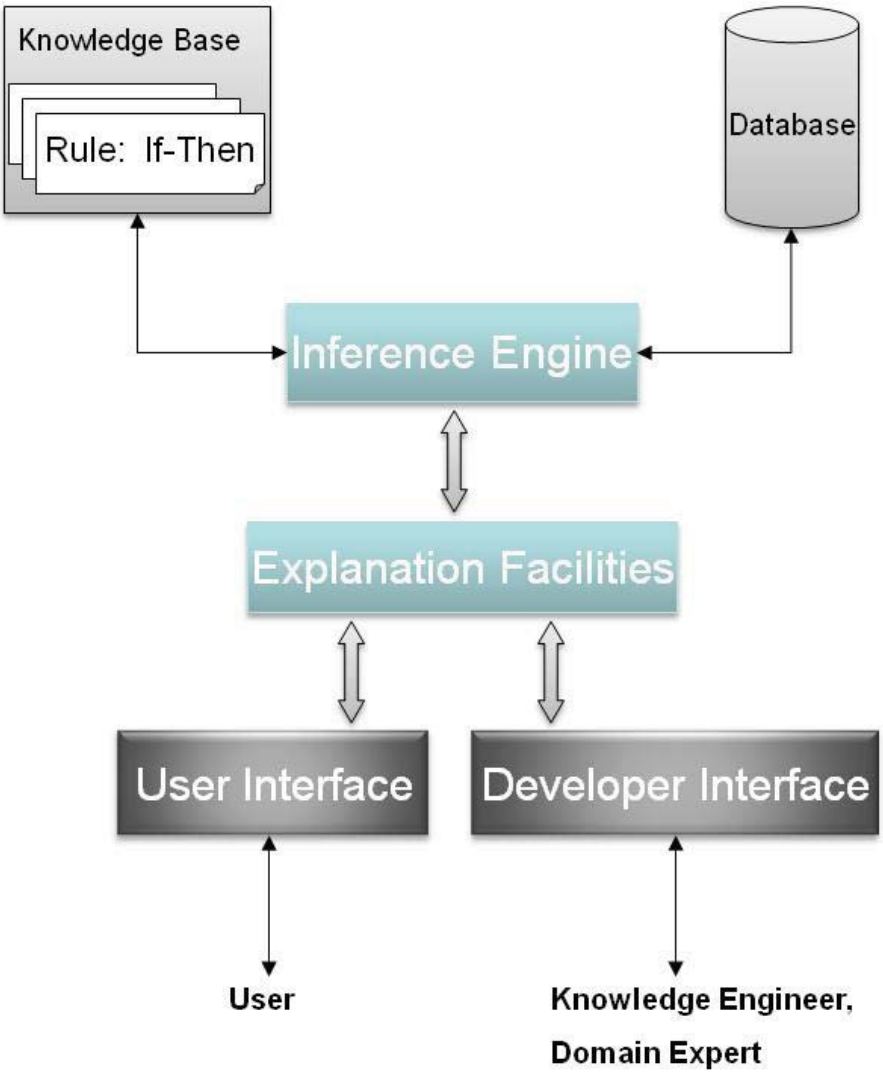


Figure 7.1 Rule-based Expert System architecture

7.2 Use Case

The eRA-CDSS was designed to computerise the comprehensive eRA guidelines that include Dose Modification Protocol, Rules for Changes in Dose/Agent and Drug Toxicity Monitoring Rules. It was also designed to provide drug toxicity predictions and alerts. The established Bayes Nets model for toxicity prediction can be realised if the causal probabilities are available and an individual patient's risk factors, laboratory results and clinical symptoms are known. Outcomes of the guidelines-based, situation-contingent recommendations and drug toxicity predictions are presented to clinicians to guide decision-making of managing RA.

7.2.1 Use Case Diagram

I used an UML (Unified Modelling Language) use case diagram (Figure 7.2) to show the functional requirements of the eRA-CDSS.

- ***Clinician:*** The individual clinician providing care to an individual patient.
- ***eEA data system:*** The clinic data system used by the clinician to support patient care. This system should support functions of the eRA-CDSS.
- ***Use case:***

  1. Apply eRA guidelines

  A Request is placed by a clinician within the eRA data system. It requires corresponding patient data to be transferred to the eRA-CDSS. Then, eRA clinic rules are triggered to generate recommendations displayed to the clinician.

  2. Predict drug toxicity risk

  Subsequently, the drug toxicity prediction model is populated to generate alerts or reminders to the clinician.

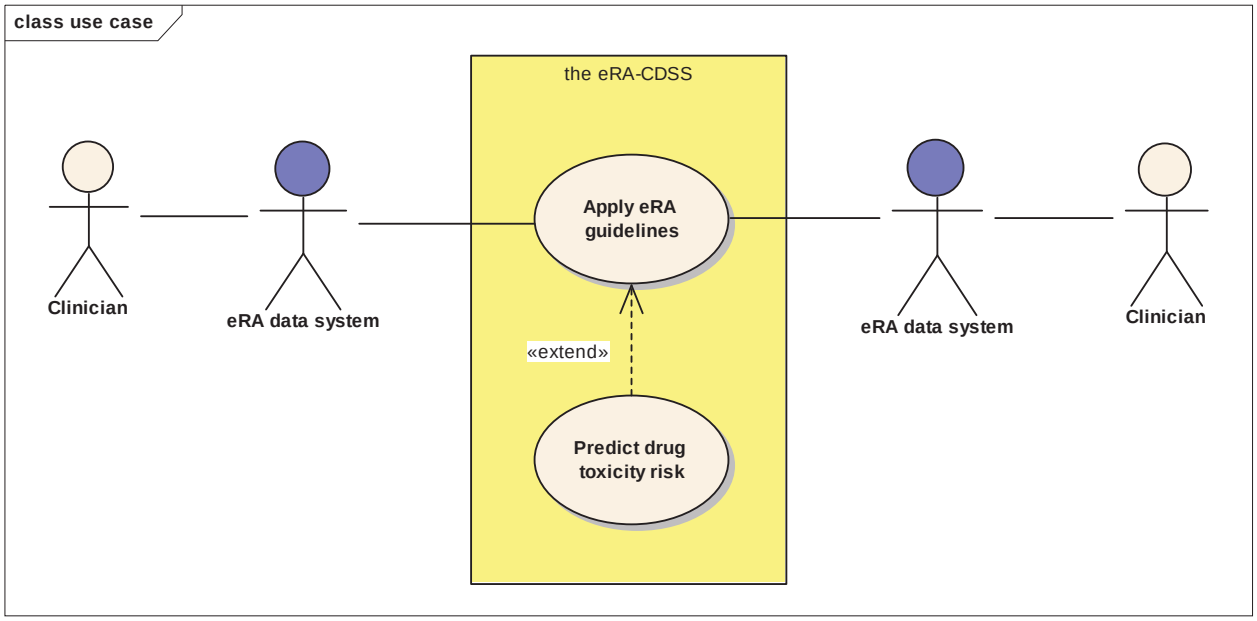


Figure 7.2 The eRA-CDSS use case

- ***Scenario and Example***

  1. Scenario

  At the eRA clinic consultation, Dr S preformed a routine check-up for Mrs Jones. Then Dr S entered the patient's reported duration of early morning stiffness, fatigue score on a 100 mm visual analogue scale (VAS), joint pain score by VAS, tender joint count and count of swollen joints or tendons into the eRA data system. The eRA data system generates a request for applying the eRA guidelines. The patient's clinical information (entered by Dr S) together with the patient's current medication information (e.g. drug dosage) and recent laboratory data such as LFT, CBE, ESR and CRP are sent to the eRA-CDSS for execution of the eRA clinical rules. Finally the eRA-CDSS presents the rule recommendations to the clinician for decision-making.

  2. Table 7.1 Sample data for the eRA-CDSS inputs and outputs

eRA-CDSS inputs	Patient clinical data	Early Morning Stiffness	15 minutes
		Fatigue	30 mm
		Joint pain	60 mm
		Joint tenderness (or pain on movement) count	3
		Soft tissue swelling (joints or tendon) count	2
	Patient current medication	MTX	15mg/week
	Patient laboratory data	LFT (AST)	Normal
		CBE (neutrophils)	Normal
		ESR	Normal
		CRP	Normal
Outputs	**Treatment recommendations:** **Increase MTX to 20mg/week, repeat laboratory test every 3 weeks**		

7.2.2 Activity Diagram

In addition to the use case diagram, I used UML activity diagram (Figure 7.3) to show how the eRA data system and the eRA-CDSS worked together to accomplish the interactions. This diagram illustrated the sequence of messages between the systems during an interaction.

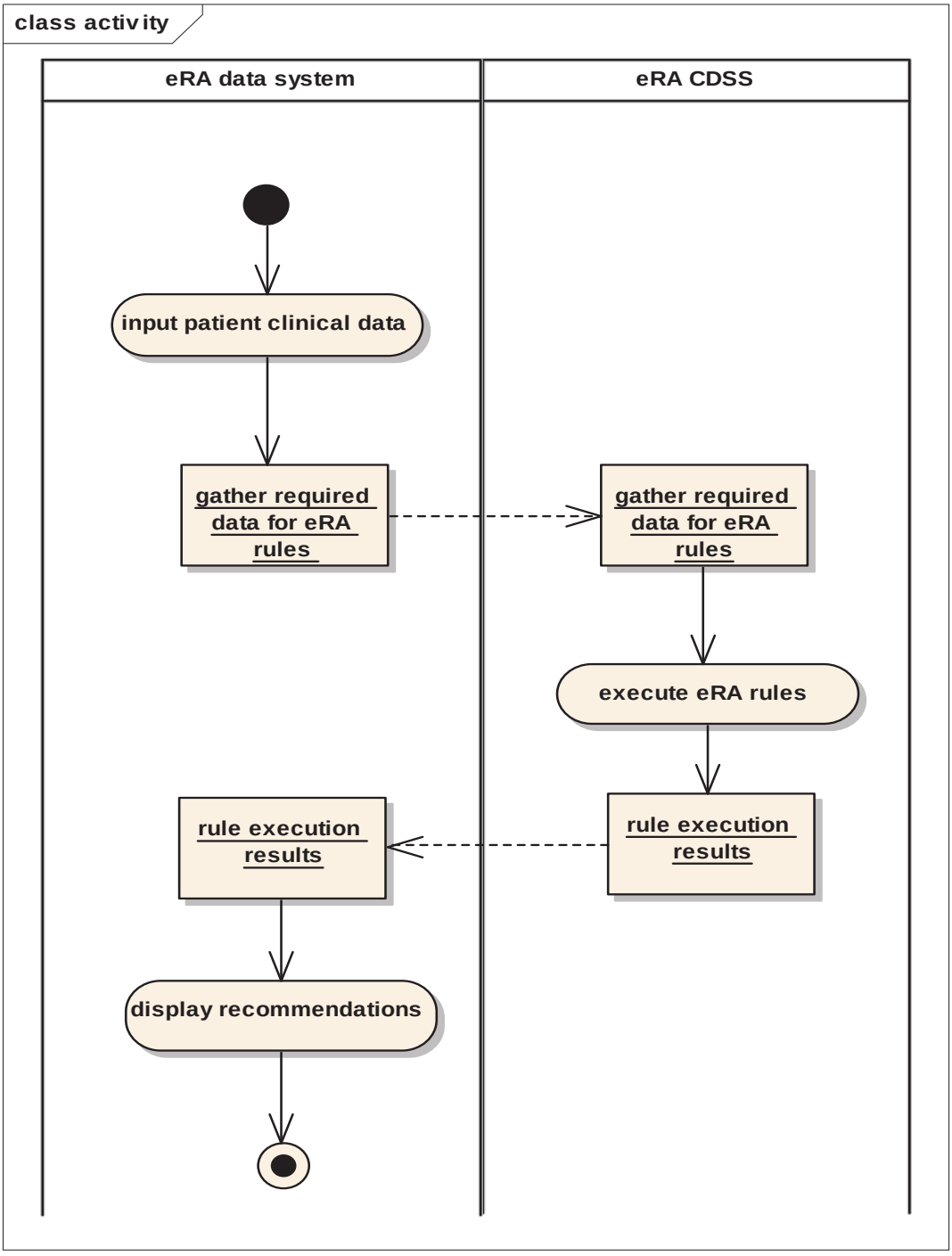


Figure 7.3 The UML activity diagram

7.3 Workflow

Understanding the clinical decision-making process, clinical workflow and dataflow is fundamental to the development of a CDSS that can be successfully integrated into clinical practice and accepted by clinicians. In order to design a CDSS that is sensitive to clinical workflow, I explored opportunities for improvements to current clinical practices that could be provided by a CDSS. Possible negative effects of the CDSS on work flows were also considered.

7.3.1 The eRA Clinic Workflow Analysis

The eRA clinic operates on every Wednesday mornings from 9am until early afternoon, with an average 20 RA patients attending. On each clinic day, one clinic nurse and 3 senior consultants (or one registrar and 2 senior consultants) work in the clinic.

The clinical workflow analysis is a collaborative process that includes people who are currently involved in the clinic and the CDSS intervention that will be integrated into the clinical workflow. Performing a clinical workflow analysis helped to identify opportunities for the intervention to provide the most immediate and quantifiable effects for the clinic. At the beginning of this study while observing the eRA clinic consultation, I analysed the workflow and dataflow of the clinic. Having identified the integration opportunity, I therefore incorporated the proposed CDSS into the clinic workflow. The following diagram (Figure 7.4) shows that the eRA-CDSS can be incorporated into the eRA clinic workflow seamlessly. The eRA-CDSS co-exists, and closely interacts with the eRA data system.

At the time of consultation, nurse and rheumatologist inputs the patient clinical data into the eRA data system. The eRA-CDSS would access patient data before executing the clinical rules. Then the eRA-CDSS would display the guideline recommendations on the computer screen to assist clinicians' decision-making when needed at the time of the consultation. Finally, computer would automatically print the patient data records along with the eRA guideline recommendations for clinicians to keep as hard copy documents.

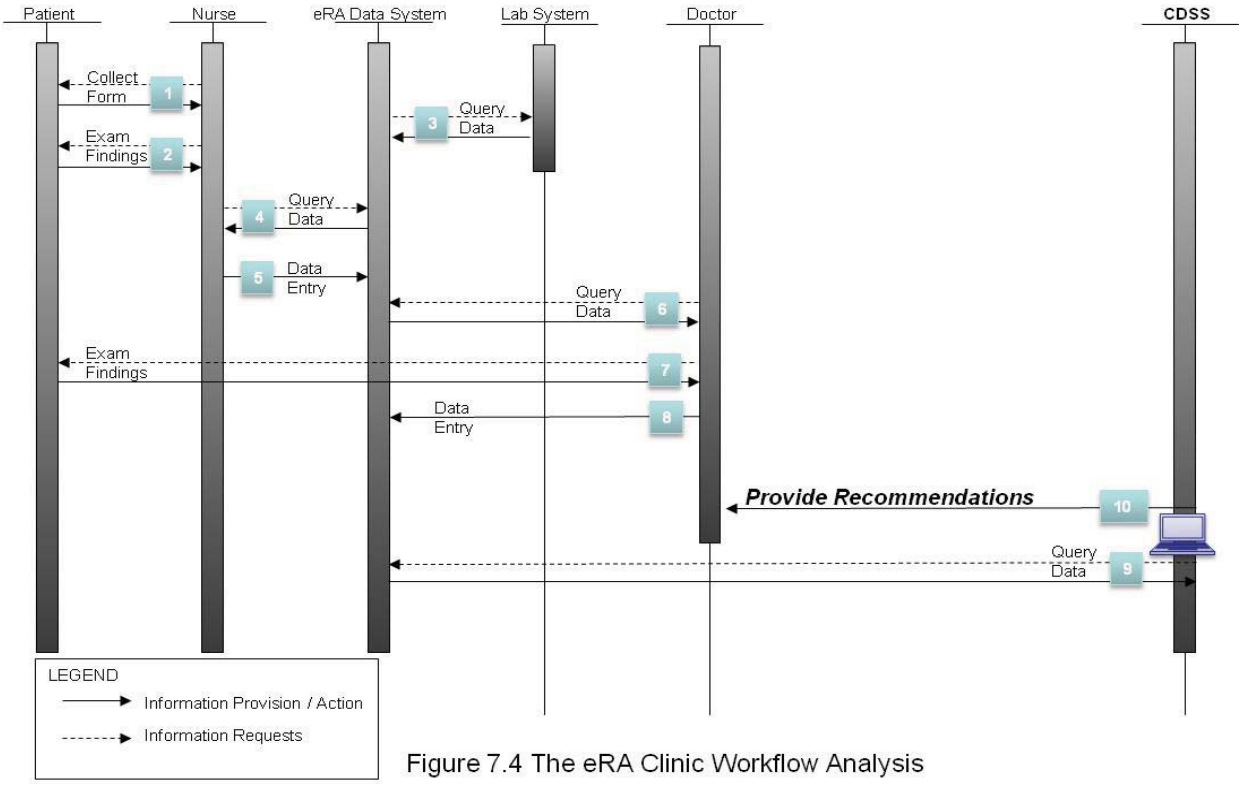


Figure 7.4 The eRA Clinic Workflow Analysis

The detailed descriptions for the corresponding numbers on Figure 7.4 were listed below:

1. Nurse collects the Vital Activities and Lifestyle Index form from the patient
2. Nurse examines the patient
3. eRA data system queries the patient laboratory results from the Lab System
4. Nurse queries data from the eRA data system
5. Nurse inputs patient data to the eRA data system
6. Doctor queries data from the eRA data system
7. Doctor examines the patient
8. Doctor inputs the patient's clinical data into the eRA data system
9. CDSS queries data from the eRA data system
10. CDSS generates guideline recommendations

7.3.2 The eRA Clinic Stakeholder Analysis

Groups of people or institutions that may significantly influence the success of an activity or project; therefore, a stakeholder analysis is a technique that can be used to identify and assess the benefits and costs of key people. I performed a stakeholder analysis for the clinicians to analyse the potential impact of incorporating the eRA-CDSS into the practice. The benefits and costs of the eRA-CDSS were identified for each stakeholder, the details of which were listed in the following table (Table 7.2).

The major cost of adopting CDSS into the current practice is the time spent on data entry using computers. However, it can be offset by the saved time spent on filling paper forms. As such, CDSS will not cost clinicians any additional effort.

Table 7.2 Stakeholder analysis of the eRA clinic

Stakeholder	Benefits	Costs	Mitigation for research
Nurse	✓ Clinical decision support ✓ Easy data access ✓ Adherence to clinical guidelines	✓ Data entry time	✓ Enter data via computers rather than filling paper forms
Physician	✓ Clinical decision support ✓ Easy data access ✓ Adherence to clinical guidelines	✓ Data entry time ✓ Reduced autonomy	✓ Enter data via computers rather than filling paper forms ✓ Workshops for agreement on guidelines ✓ Reduced decision-making stress ✓ More structured practice environment
Patient	✓ Reinforced patient monitoring ✓ Improved care	Nil	Nil

7.4 The eRA-CDSS Architecture

7.4.1 Conceptual View

The core component of the eRA-CDSS is the inference engine. It executes the rules of the eRA clinical guidelines and implements the established drug toxicity prediction models. The corresponding rule can be triggered automatically by retrieving patient data from the CPR (e.g. the Lab System), or by receiving patient data entered by the clinician. If the rule conditions are satisfied, it is executed. Finally, the CDSS delivers the guidelines-based recommendations and the probabilities of developing drug toxicity to the clinicians for decision-making. Figure 7.5 shows a conceptual view of the eRA-CDSS architecture.

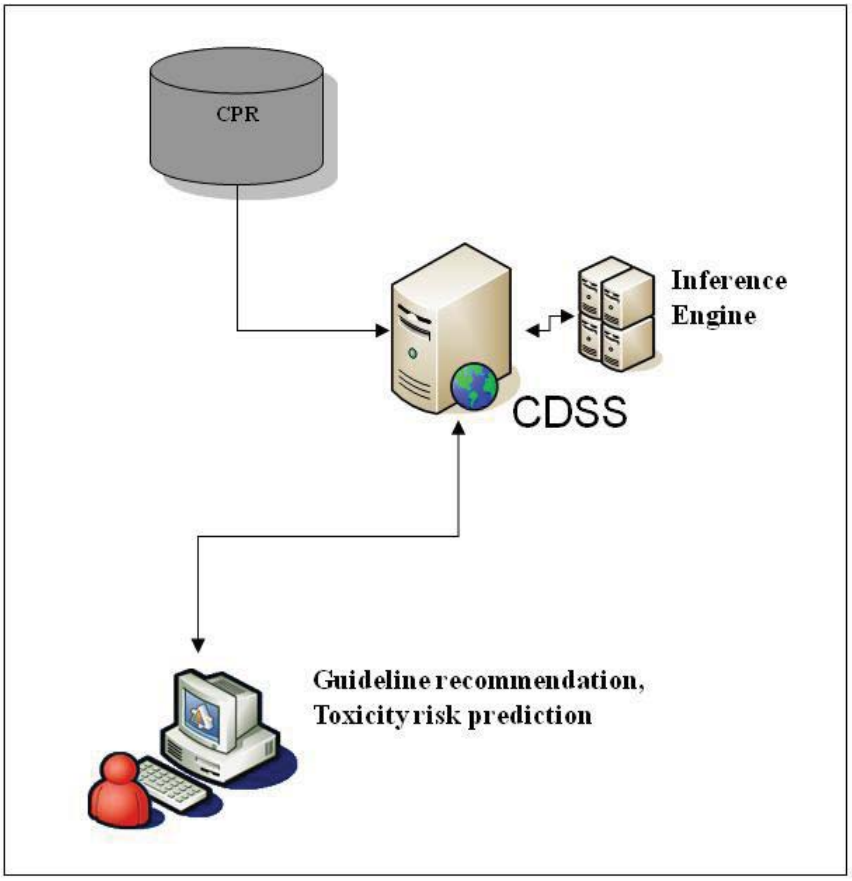


Figure 7.5 The conceptual view of the eRA-CDSS architecture

7.4.2 Logical View

The design of the eRA-CDSS was based on a multi-tiered Service Oriented Architecture (SOA). The front-end user interface and the back-end services are loosely coupled. A loosely coupled architecture allows you to replace components, or change components, without having to make reflective changes to other components in the architecture/systems. The CDSS back-end services are exposed as a set of web services via the Internet. This model provides great flexibility for clinicians in accessing the CDSS services when the CDSS front-end is connected to the Internet. Figure 7.6 showed a logical view of the eRA-CDSS architecture.

The CDSS front-end Graphic User Interface (GUI) is implemented as a Windows desktop application. It retrieves patient data from CPR, such as the eRA Data System or the Lab System, and submits these data to the CDSS back-end service via the Internet. The CDSS back-end web service defines the interface between the front-end and back-end such as formats for exchanging data. The inference engine applies a predefined rule set to the supplied data and executes the rules. The data access logic performs database operations. It retrieves a nominated rule set from the back-end database and passes it to the inference engine. The Service Framework contains shared services to support all the back-end components including auditing, exception management, security and reporting.

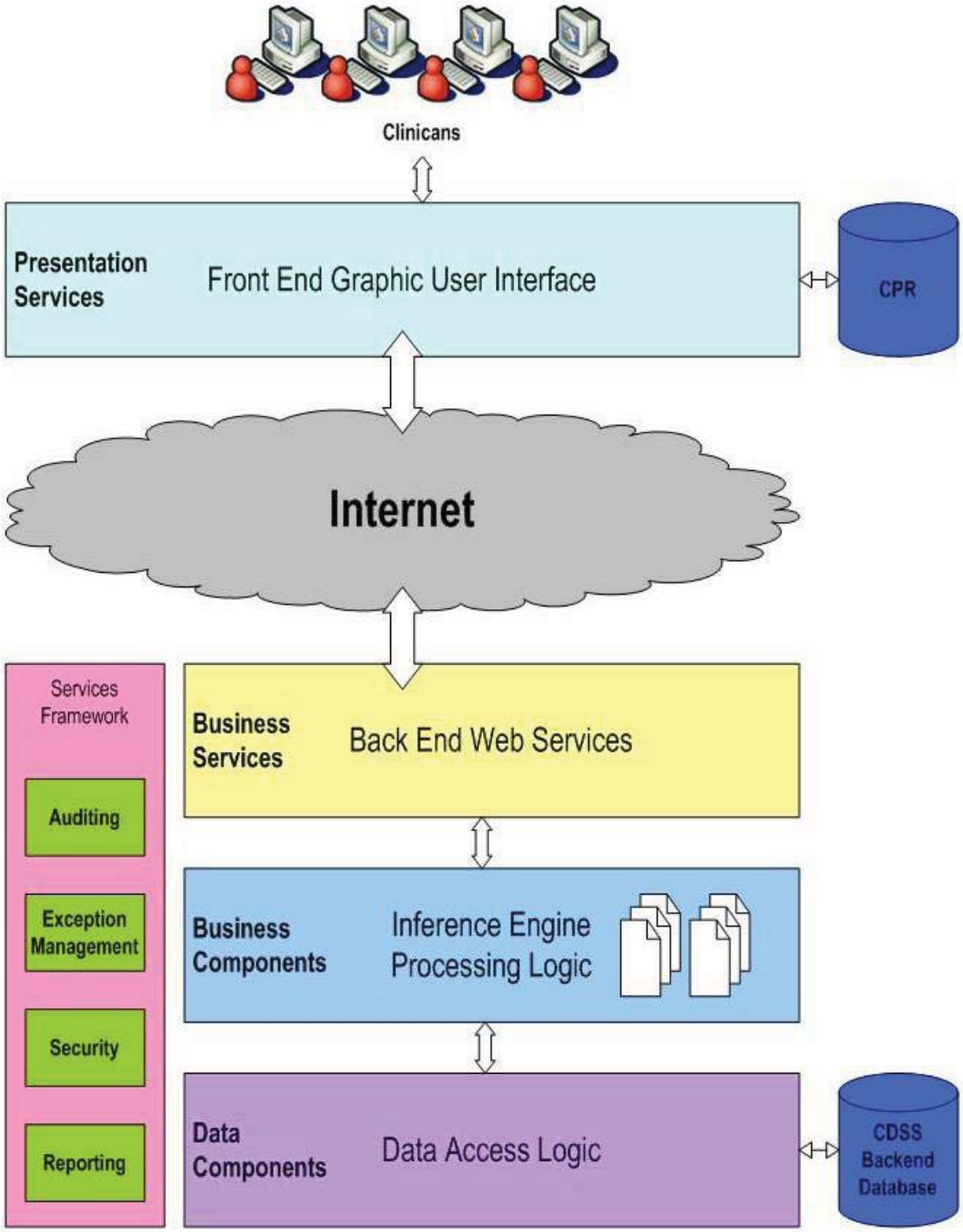


Figure 7.6 The logical view of the eRA-CDSS architecture

7.4.3 The eRA Data System with Inbuilt CDSS GUI Snapshot

The eRA-CDSS co-exist with the eRA Data System. The eRA Data System with inbuilt CDSS will have five key business functions. They are (1) real-time patient data entry, (2) graphical presentation of data trends, (3) generation of reports of patient data, (4) delivery of guideline recommendations, and (5) prediction of probabilities of developing drug toxicity.

I have included some sample Graphic User Interfaces (GUI) snapshots (Figures 7.7-7.9) to provide a general overview of the developed System. These GUIs were designed to assist clinicians to interact with the system in a user-friendly manner, therefore to minimise cost of time.

Figure 7.7 demonstrates a real-time data entry screen for joint scores. Clinicians can record tender joints and swollen joints (required by Dose Modification Protocol) by simply clicking the corresponding joints illustrated on the screen. The system automatically calculated tender joint count and swollen joint count for the clinician. It then displayed the results on the screen. It also passed the data to the eRA-CDSS for rule execution. DAS can be calculated for clinicians if its required data had been provided to the system.

Figure 7.8 shows the key patient clinical indexes (e.g. DAS) and the laboratory data (e.g. CRP). These data are displayed in graphical trends. The patient's clinical indices and laboratory data from the antecedent period were plotted on the graph. These visual graphic trends can help clinicians foresee the future clinical status of a patient. In addition, the six laboratory variables including CRP, ESR, neutrophils, ALT, AST and creatinine are needed by the eRA guidelines; therefore, they are to be passed to the eRA-CDSS for rule execution.

Figure 7.9 displays a screen of CDSS recommendations. The eRA-CDSS executed the eRA clinical rules upon receiving the required patient data. Then it passed the guideline recommendations to the eRA Data System for demonstration. As shown in the Figure 7.9, the scheduled routine visits, scheduled blood tests and

recommendations on medication changes were generated by the eRA-CDSS. However, clinicians have the options to accept or ignore the CDSS recommendations by checking ‘Agree’ or ‘Disagree’ checkboxes. The eRA Data System has the potential to record clinicians’ responses to the CDSS recommendations. These data can be audited or analysed in the future for guideline compliance analysis or guideline evaluation.

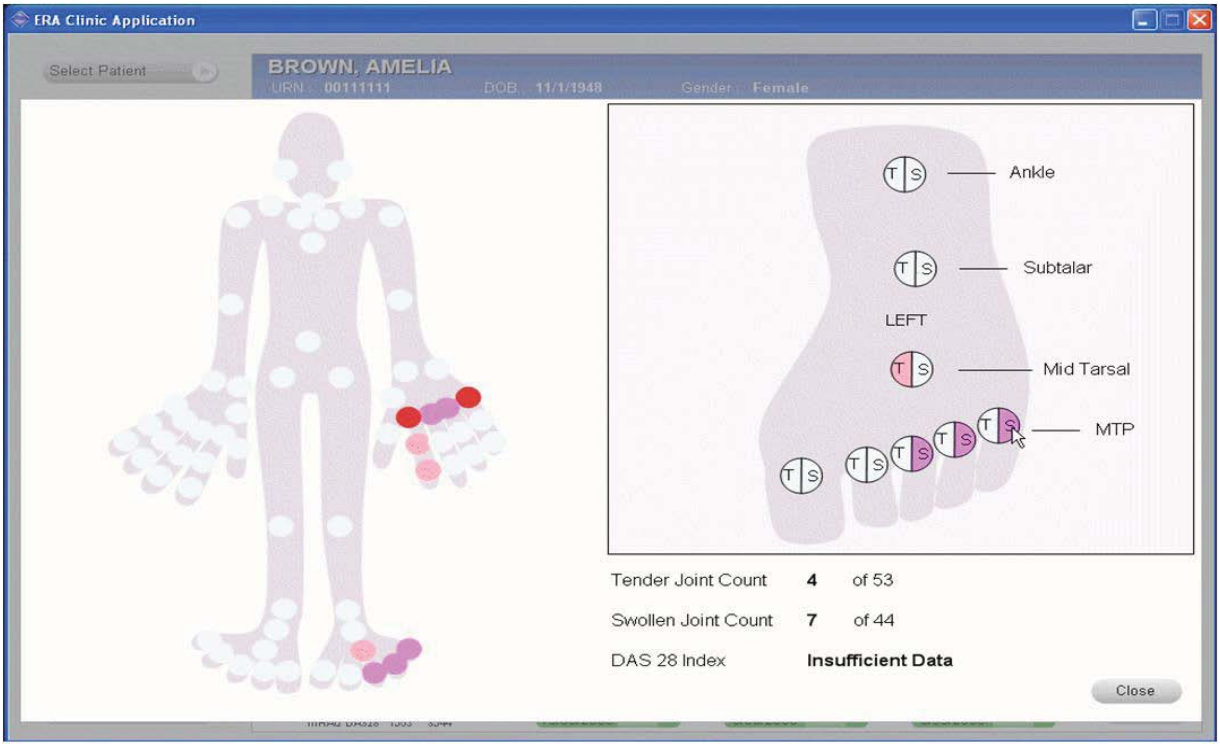


Figure 7.7 Real-time entry for joint scores

Figure 7.8 Graphical trends of patient clinical data and laboratory data

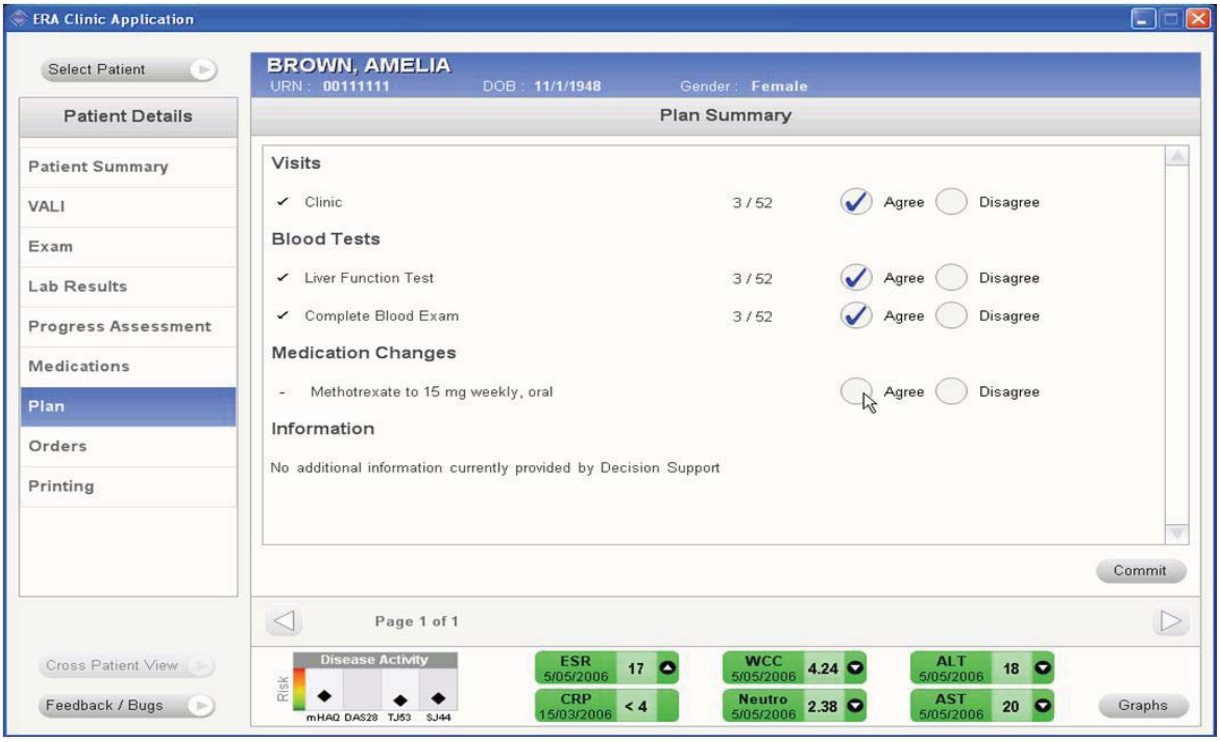


Figure 7.9 CDSS decision regarding treatment and follow up plan

8 Guideline Verification

Adherence to CPGs can improve the quality of clinical decision-making. Compliance with guidelines in the eRA clinic, for which eRA clinicians incorporate **Drug Toxicity Monitoring Rules** and **Rules for Changes in Dose/Agent** into their practice, has never been studied. The level of guideline compliance addresses the issues in guideline acceptance, which is fundamental for developing a clinically accepted CDSS.

In order to test the benefits of the guideline automation system in a real clinical setting and to ensure wide applicability for the future use of the CDSS in the eRA clinic or other clinical settings, I conducted a questionnaire to test the acceptance of the newly established RA management rules. The questionnaire provided valuable information not only for future guideline refinement and development, but also for future CDSS improvement.

8.1 Method - Questionnaire

The concordance between clinicians' decisions and CDSS recommendations can be used to gauge the acceptance of computerised guidelines by clinicians in making clinical decisions. In early 2007, I conducted a questionnaire-based assessment to assess the acceptance of the guidelines amongst two groups of rheumatologists (an eRA clinic group and a non-eRA clinic group). The questionnaire was designed to test the acceptance of the guideline recommendations generated by CDSS, to locate the gaps between guidelines and practice, and to provide information that may be used for the development of the CDSS tool with regard to broader clinical acceptability.

I designed 16 questions based on 16 real patient case scenarios extracted from eRA clinical records. I ran these 16 cases through the CDSS and retrieved the CDSS recommendations. The objective of the questionnaire was to collect the treatment decisions from the rheumatologists for the 16 patient case scenarios in order to measure the differences between the doctors' decisions and computerised guideline recommendations, and to analyse the results.

8.2 Participant & Sample Size

- **Characteristics of participants**

A total of eight rheumatologists (n=8) participated in this questionnaire study, including 7 senior consultants and 1 rheumatology advanced trainee. Four rheumatologists working in the eRA clinic were grouped in the eRA group (D1-D4); the other four rheumatologists who do not work in the eRA clinic were grouped in the non-eRA group (D5-D8). The non-eRA group received no pre-test training regarding the CDSS rules. Comprehension of the eRA guidelines in the eRA group is better compared with the non-eRA group because the rheumatologists are more familiar with the eRA rules and protocol.

- **Characteristics of the patient cases**

Patients over the age of 18 diagnosed with RA according to the 1987 revised American College of Rheumatology (ACR) criteria, who are receiving treatment with triple therapy (MTX, SSA and HCQ) for early RA.

8.3 Cases Selection

The questionnaire was designed to test compliance with eRA guidelines in a simulated clinical setting using selected patient cases. From late 2006, I started to read through eRA clinic correspondence to referring doctors for the period from early 2002 until October 2006. There were total of 923 RA patient visits to the eRA clinic during the period. I carefully selected 16 real patient cases based on the fact that these cases have scenarios that can trigger the rules included in Drug Toxicity Monitoring Rules or in Rules for Changes in Dose/Agent. Among the 16 cases, 7 cases triggered the rules in Rules for Changes in Dose/Agent (from here on I shall call them 'triple therapy cases'), and 9 cases triggered the rules in Drug Toxicity Monitoring Rules (from here on I shall call them 'toxicity cases').

8.4 Questionnaire Design

I designed the questionnaire to include the 16 selected patient case scenarios. I manually retrieved case associated clinical data and laboratory data from the eRA clinic database. In the questionnaire, each case is represented as a real case abstract, including the patient's clinical, laboratory and therapy information.

The questionnaire asked the rheumatologists to use the provided information to make a decision on whether treatment should be changed, and if so, how. Each case abstract had two copies; one copy included the minimum clinical variables required by the RA management rules (CDSS input), the other copy provided patient clinical information (e.g. symptoms regarding drug side effects other than GI symptoms and laboratory tests) in addition to the minimum clinical variables required by the RA management rules. The rheumatologists were asked to respond to both copies in each case. Their decisions on the copy with the minimum CDSS input were compared to the CDSS outputs, and the differences were analysed. Whether the decision made by clinicians changed between the two questionnaire copies was also analysed. The questionnaire samples are shown in the Appendices (questionnaire1 includes the minimum CDSS input; questionnaire2 provides extra patient clinical information).

8.5 Intervention

A preliminary version of the CDSS that automates comprehensive eRA guidelines has been implemented. The eRA-CDSS computerises Dose Modification Protocol, Rules for Changes in Dose/Agent and Drug Toxicity Monitoring Rules. It was used to generate drug regimen recommendations, drug dosage and patient monitoring plans for the 16 patient cases. I compared these CDSS generated recommendations with the decisions from the questionnaire.

8.6 Evaluation

For the purpose of evaluating and analysing the results, I defined a rule for grouping the data. I defined five decision categories, which were (1) stop/hold, (2) decrease, (3) no changes made, (4) increase/restart, and (5) add. The questionnaire results and CDSS outputs were grouped into these categories. I further arranged these five categories into a predefined decision sequence, which ranges from a cautious or conservative decision to an assertive decision. I also assigned a distinct value to each decision category (Figure 8.1).

Conservative ← → Assertive

Stop/hold	Decrease	No changes made	Increase/restart	Add
-2	-1	0	1	2

Figure 8.1 Predefined decision categories with distinctive assigned values

By assigning a distinct value to each decision category, I was able to compare and measure the metric distance between the rheumatologists' decisions and CDSS recommendations. I defined a Distance Calculating Formula* to calculate the metric distance as follows:

*Distance = Doctor-CDSS

Comparing the gaps in decision-making by grouping the data into predefined decision categories does not distinguish between differences such as dosage and various drug differences within a particular category. In order to analyse the dosage and various drug differences within the decision categories, between rheumatologists and CDSS, I calculated two sets of compliance rates; the first set of compliance rates considers both dosage difference and various drug differences; the second set of compliance rates considers various drug differences, but not the dosage difference.

8.7 Statistical Analysis

I applied Kappa statistics to analyse the agreement between each rheumatologist's decision and CDSS output for the 16 patient cases. Kappa is an index of observer agreement, which indicates the degree of agreement over and above that which would be expected by chance alone (Table 8.1).

Table 8.1 Agreement of categorical measurements

Kappa	Strength of agreement
0.00	Poor
0.01-0.20	Slight
0.21-0.40	Fair
0.41-0.60	Moderate
0.61-0.80	Substantial
0.81-1.00	Almost perfect

I calculated the compliance rate for each individual rheumatologist by comparing the rheumatologist's decision with the recommendations generated by the CDSS. I applied two sample mean comparison tests to compare the mean compliance rate between the two groups of rheumatologists.

This study used Stata 8 software (State Corp., College State, TX, USA) to analyse the data. Binary variables for five different drug treatment strategies (stop/hold, decrease, no changes made, increase/restart and add) were used to calculate Kappa.

8.8 Results

A total of eight rheumatologists from the two groups completed the questionnaire. I collected the rheumatologists' decisions on the 16 patient cases, and retrieved the CDSS output for the same 16 cases. I measured the metric distance by comparing the rheumatologists' decisions with the CDSS recommendations according to the predefined decision categories and Distance Calculating Formula. I also calculated the compliance rate for the combined 16 cases; 7 triple therapy cases and 9 toxicity cases respectively.

1. Metric distance

   The Distance Calculating Formula was applied to measure the distance between the decisions made by rheumatologists and CDSS recommendations. One sample t-test shows that there was no statistical difference between the eRA group and the CDSS (mean distance=0.0313, P=0.7879); but results for the non-eRA group were significantly different when compared with the CDSS (mean distance=-0.4219, P=0.0009). In addition, the mean distance between the eRA group and the CDSS is statistically different, compared to the distance between the non-eRA group and the CDSS (P = 0.0079) (Figure 8.2).

   Figure 8.3 shows the metric distance between decisions made by the two groups of rheumatologists and the recommendations generated by the CDSS. The columns represent the metric distance calculated by the Distance Calculating Formula (1-7 are triple therapy cases, 8-16 are toxicity cases). In order to show the dosage and various drug differences between the rheumatologists and the CDSS, I added arrows to represent the differences.

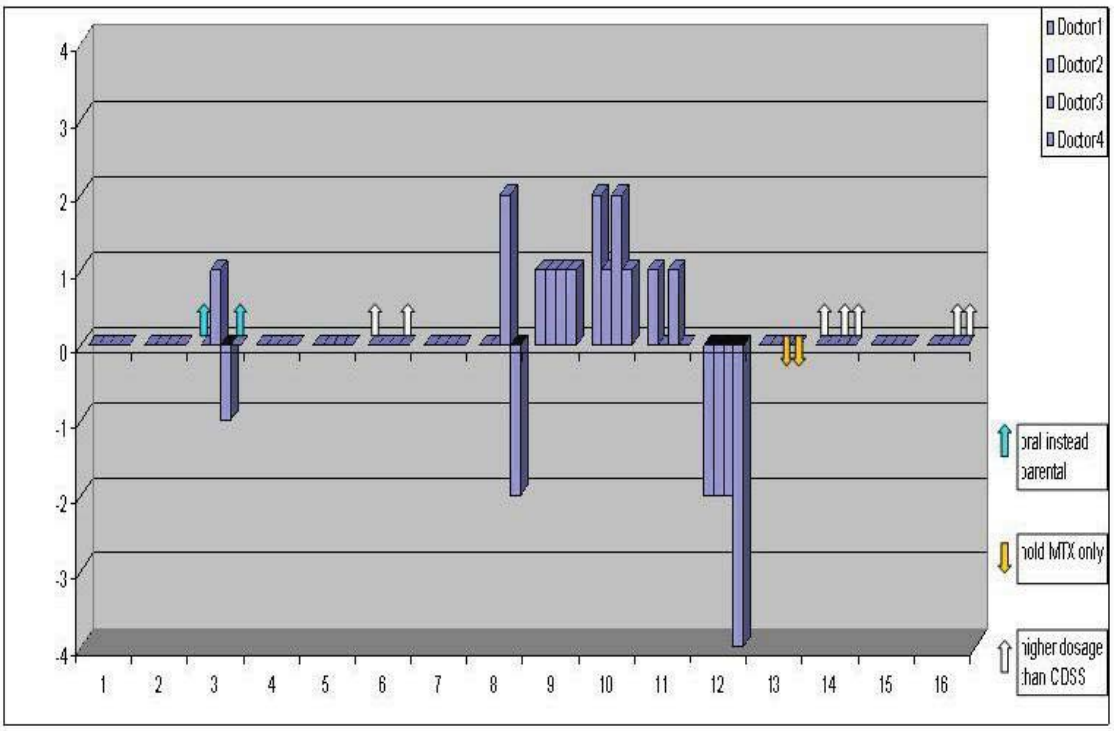
   Interestingly, Figure 8.3 shows all the rheumatologists responded conservatively on case 12. I reviewed the clinical scenario of case 12 which stated the patient had two consecutive mild toxicity events (mild elevated ALT 87 and 62); the patient's disease activity was not well controlled according to the eRA Dose Modification Protocol (Tender joint 7, swollen joint 2, Fatigue 33); the patient was on MTX 25

mg. According to the RA management rules, a new drug leflunomide (Arava) should be added to the drug regimen. However, the decisions made by the rheumatologists were to either keep the treatment unchanged, or reduce the dosage of MTX, or hold MTX.

This is an interesting scenario in which the conservative approach is to ignore the imperatives for better disease control in favour of avoiding possible aggravation of the out of range blood results. As addition of leflunomide would be subject to close monitoring of liver enzymes (three weekly or potentially more often) and the drug could be cleared promptly with Questran if needed due to unwanted effects (including rise in LFTs), addition of leflunomide 10mg daily would have been reasonable. It is possible that the patient was subjected to greater risk from disease when short-term risks for toxicity were acceptably low, testable and by no means inevitable. It is perhaps an example of how considered opinion regarding risks and strategy (testing of drug subject to potential modification of drug dose and timing of review) can benefit from prior considered opinion based on scenario analysis.

Figure 8.2 Distance comparison between the eRA group and the non-eRA group

eRA group



Non-eRA group

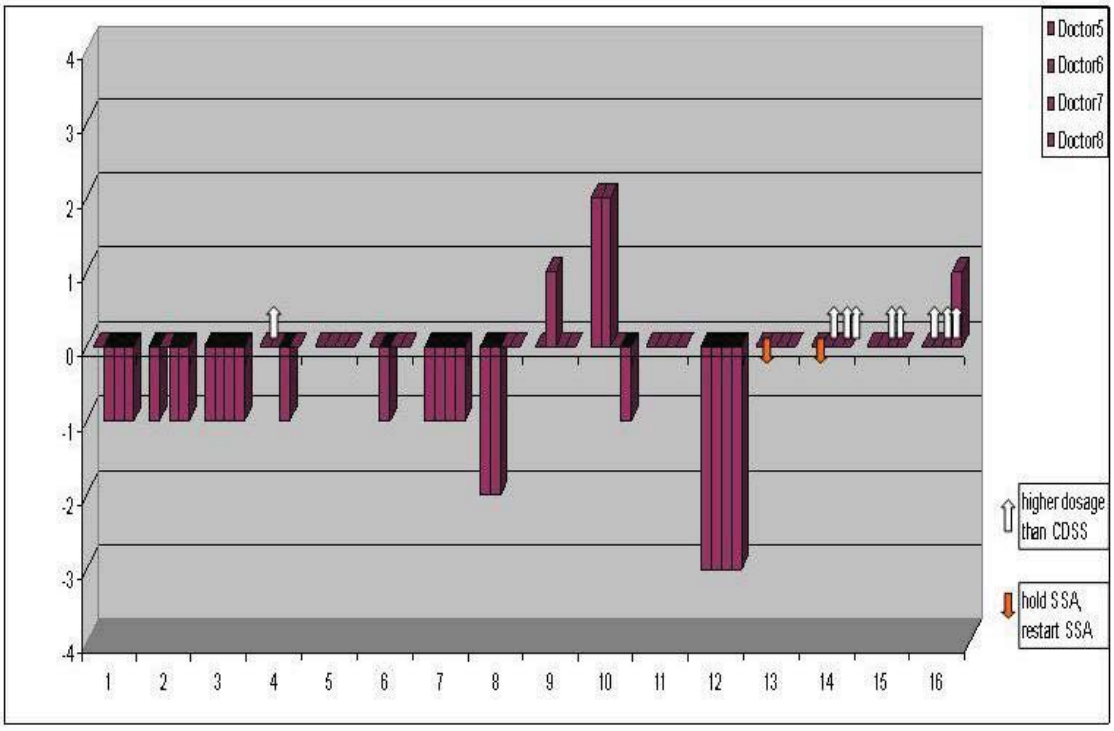


Figure 8.3 Distance between rheumatologists' decisions and CDSS recommendations

2. Kappa statistics analysis

I applied Kappa statistics to analyse the overall agreement between the 8 rheumatologists and the CDSS on the 16 cases. Table 8.2 shows the Kappa analysis results.

Three rheumatologists from the eRA group have substantial agreement (kappa statistics 0.6000 and 0.6098; one has moderate agreement (kappa statistics 0.4217). No rheumatologist from the non-eRA group has substantial kappa values; three rheumatologists from the non-eRA group have moderate agreement (kappa statistics 0.4947, 0.4839 and 0.4286); one has slight agreement (kappa statistics 0.2727).

Table 8.2 Kappa analysis results for the agreement

		Agreement	Kappa	Standard error
eRA group	D1	75.00%	0.6000	0.1521
	D2	75.00%	0.6098	0.1568
	D3	62.50%	0.4217	0.1510
	D4	75.00%	0.6098	0.1370
non-eRA group	D5	62.50%	0.4839	0.1402
	D6	50.00%	0.2727	0.1477
	D7	62.50%	0.4947	0.1261
	D8	56.25%	0.4286	0.1230

3. Compliance rate analysis

I calculated the compliance rate by comparing whether the decisions made by the rheumatologists fell into the same decision categories as the CDSS generated recommendations, as well as by comparing the drug dosage and various drug differences between the rheumatologists and the CDSS. Table 8.3 shows the compliance rate of the eight individual rheumatologists for combined cases, triple therapy cases and toxicity cases respectively. Table 8.4 and Figure 8.4 show the mean compliance rate comparison between the two groups for combined cases, triple therapy cases and toxicity cases respectively.

Table 8.3 Mean of compliance with CDSS for individual rheumatologists

		Combined	Rules for Changes in Dose/Agent	Drug Toxicity Monitoring Rules
number of cases		16	7	9
compliance rate	D1	56.25%	71.43%	44.44%
	D2	75.00%	85.71%	66.67%
	D3	43.75%	85.71%	11.11%
	D4	43.75%	71.43%	22.22%
	D5	43.75%	57.14%	33.33%
	D6	25.00%	28.57%	22.22%
	D7	43.75%	28.57%	55.56%
	D8	50.00%	42.86%	55.56%

Table 8.4 Mean of compliance with CDSS for eRA group and non-eRA group

	eRA group	**non-eRA group**	**P value**
combined	0.5469	0.4063	0.17550
triple therapy	0.7857	0.3929	0.00270
toxicity	0.3611	0.4167	0.72150

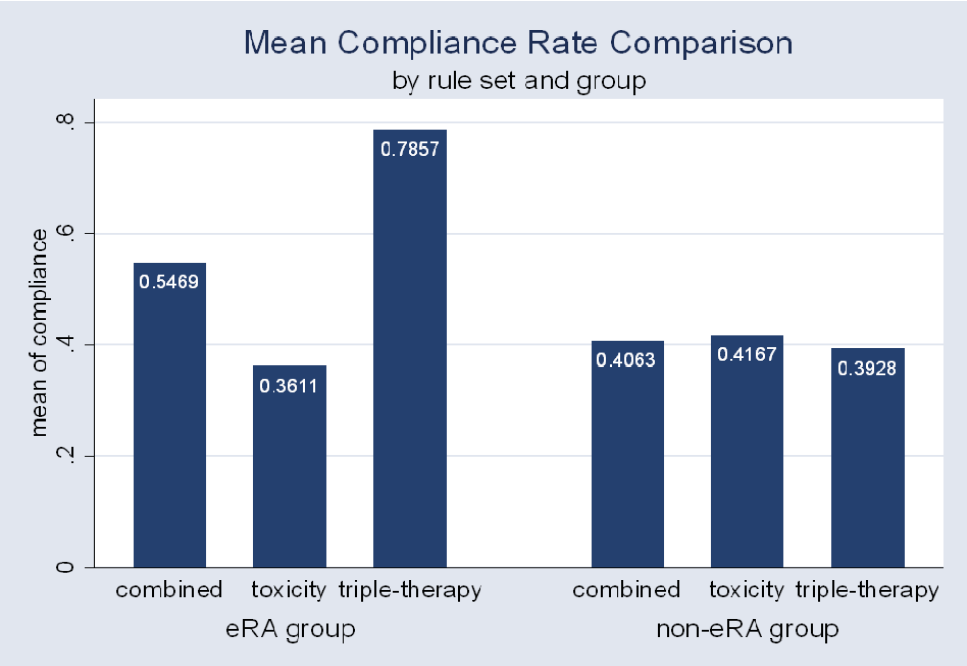


Figure 8.4 Mean of compliance comparison between eRA group and non-eRA group

a) Inner group comparison

In the eRA group, the compliance rate for the triple therapy rule is statistically higher than the compliance rate for toxicity rule (0.7857 vs. 0.3611, P = 0.0171). In the non-eRA group, no difference was found between the compliance rates for triple therapy rule and toxicity rule (0.3929 vs. 0.4167, P = 0.8324).

b) Inter group comparison

There is no statistical difference in mean compliance rates between the eRA group and the non-eRA group in combined cases (0.5469 vs. 0.4063, P = 0.1755). The mean compliance rate of the eRA group for triple therapy is significantly higher than the mean compliance rate of the non-eRA group (0.7857 vs. 0.3929, P = 0.0027). There is no statistical difference between the eRA group and the non-eRA group for toxicity rule (0.3611 vs. 0.4167, P = 0.7215).

4. I calculated the compliance rate again by assessing whether the decisions made by the rheumatologists fell into the same decision categories as the CDSS generated recommendations by comparing the direction change in drug dosage if any while tolerating dosage difference between rheumatologists and the CDSS. Table 8.5 shows the compliance rate for the eight individual rheumatologists in combined cases, triple therapy cases and toxicity cases respectively. Table 8.6 and Figure 8.5 show a comparison of the groups' mean compliance rates in combined, triple therapy and toxicity cases respectively.

Table 8.5 Mean of compliance with CDSS by decision category (dose-tolerant) for individual rheumatologists

		Overall	Triple therapy	Toxicity
number of cases		16	7	9
compliance rate	D1	75.00%	100.00%	55.56%
	D2	75.00%	85.71%	66.67%
	D3	56.25%	85.71%	33.33%
	D4	75.00%	100.00%	55.56%
	D5	43.75%	57.14%	44.44%
	D6	43.75%	42.86%	44.44%
	D7	56.25%	28.57%	77.78%
	D8	56.25%	42.86%	66.67%

Table 8.6 Mean of compliance with CDSS by decision category (dose-tolerant) for eRA group and non-eRA group

	eRA group	**non-eRA group**	**P value**
combined	0.7031	0.5000	0.01390
triple therapy	0.9286	0.4286	0.00040
toxicity	0.5278	0.5833	0.62800

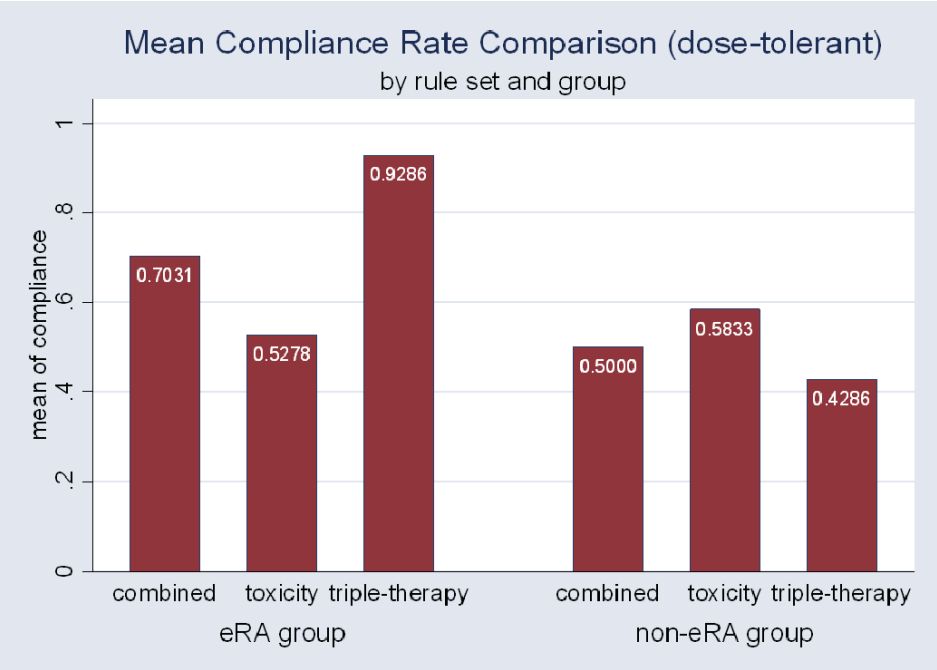


Figure 8.5 Mean of compliance comparison (tolerating differences in doses) between eRA group and non-eRA group

a) Inner group comparison for dosage tolerated compliance

In the eRA group, the compliance rate for triple therapy rule is statistically higher than the compliance rate for toxicity rule (0.9286 vs. 0.5278, P = 0.0117). In the non-eRA group, no difference was found between the compliance rates for triple therapy rule and toxicity rule (0.4286 vs. 0.5833, P = 0.3355).

b) Inter group comparison

The eRA group has a statistically higher mean compliance rate in comparison to the non-eRA group in combined cases (0.7031 vs. 0.5, P = 0.0139). The mean compliance rate of the eRA group for triple therapy is significantly higher than the mean compliance rate of the non-eRA group (0.9286 vs. 0.4286, P = 0.0004). There is no statistical difference between the eRA group and the non-eRA group for toxicity rule (0.5278 vs. 0.5833. P = 0.6280).

5. By calculating the complete compliance rate (drug compliance and dosage compliance) and dose-tolerant compliance rate (drug compliance but tolerating dosage difference) for the two groups in 16 combined cases; 7 toxicity cases and 9 triple therapy cases, the results reveal a higher dose-tolerant compliance rate than a complete compliance rate (Figure 8.6). The statistical analysis shows that the mean dose-tolerated compliance rate of the eRA group is significantly higher than the complete compliance rate for triple therapy cases. (0.9286 vs. 0.7857, P value = 0.0498). However, there is no statistical difference found in toxicity cases and combined cases.

6. In the second copy of the questionnaire extra information, such as patient additional drug toxicity related symptoms other than GI side effects and extra laboratory test results, was provided, which influenced clinicians to change their decisions on some cases. Among the 128 decisions made by 8 rheumatologists on 16 patient cases, a total of 24 decisions had been changed upon the questionnaire provided extra information, twelve in the eRA group and 12 in the non-eRA group. The rate was 19% for both groups. However, the changes were spread out among the cases and also varied between the two groups. It underlines more patient cases are needed for further investigation. The yellow person like symbol in Figure 8.7 represents the change on the corresponding cases.

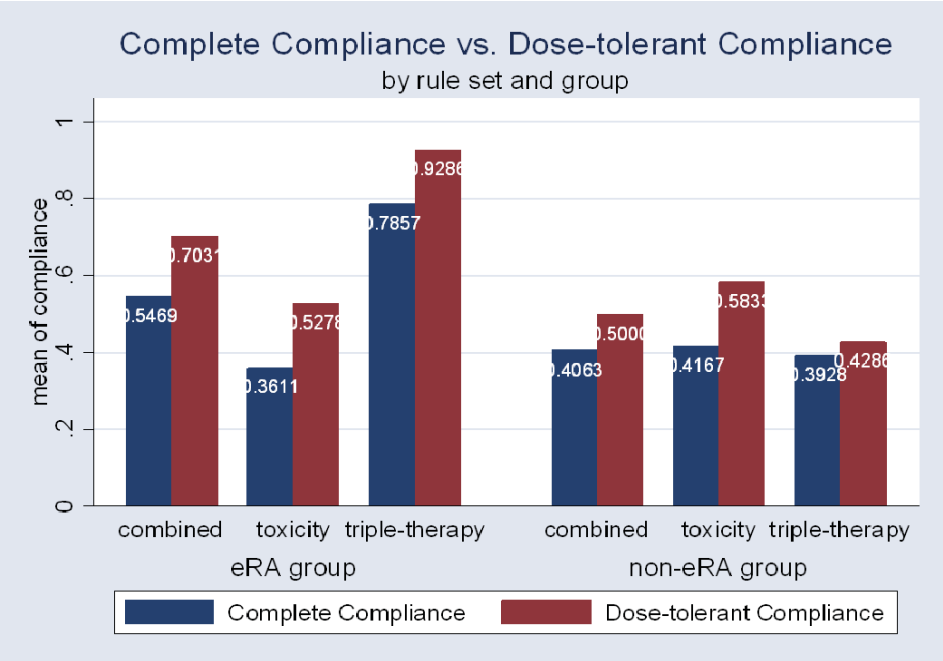


Figure 8.6 Mean of compliance comparison between complete compliance and dose-tolerant compliance

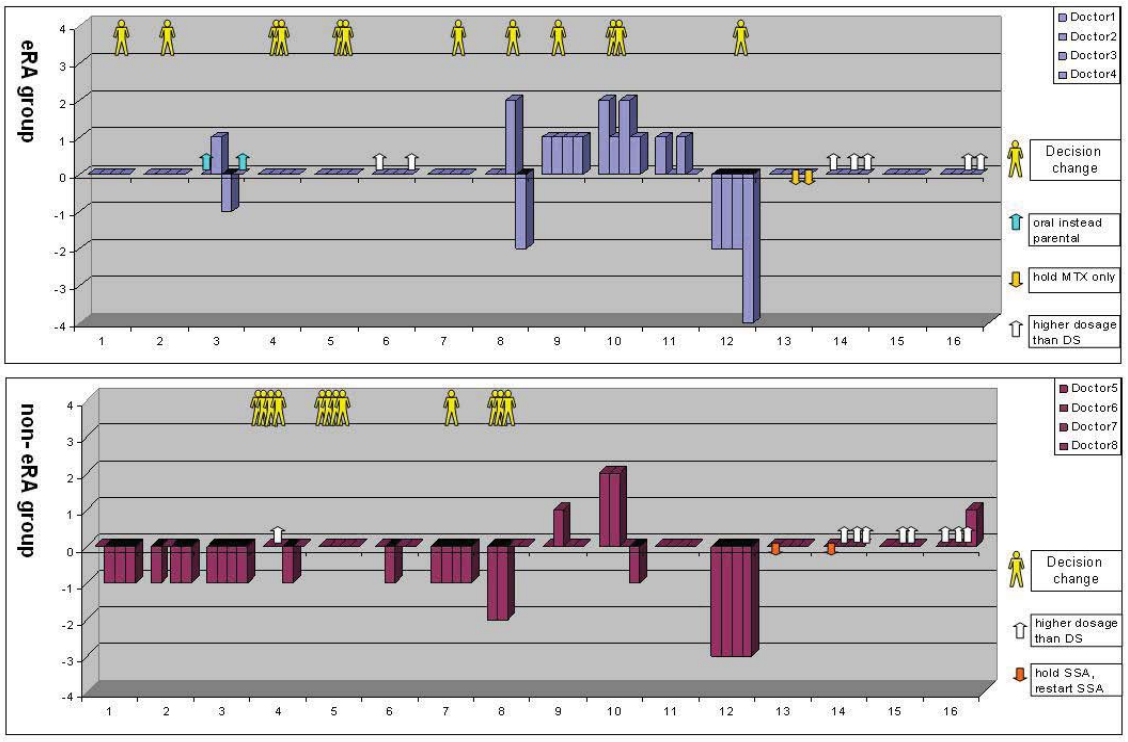


Figure 8.7 Changing decision cases of the eRA groups and non-eRA group

From the statistical analysis, it was concluded that:

- Rheumatologists from the non-eRA group were more conservative in their practice relative to CDSS recommendations and eRA rheumatologists
- The eRA group had better agreement with CDSS recommendations compared to the non-eRA group
- The eRA group had a higher mean compliance rate in the triple therapy cases than the toxicity cases; whereas, in the non-eRA group, the mean compliance rate for the triple therapy cases was not statistically different from the mean compliance rate for the toxicity cases
- The eRA group had a higher mean compliance rate in triple therapy cases compared to non-eRA group, but there was no difference between the two groups in the mean compliance rate for toxicity cases
- In both groups, analysis of dose-tolerant on drug dosage yielded higher compliance between decisions made by the rheumatologists and CDSS generated recommendations
- In both groups, providing additional patient information caused changes in decision

Based on the statistical analysis results, I found that the rheumatologists from the non-eRA group practiced more conservatively compared with the rheumatologists from the eRA clinic (P value = 0.0079). In addition, the eRA group had a higher mean compliance rate in triple therapy cases compared to the non-eRA group. The combined results verify that CDSS guidance concurs with interpretation of eRA management rules for dosage adjustment by clinicians familiar with their application, and well accepting the rules. Compliance with guidelines leads to more consistent, evidenced based clinical decision-making in the eRA clinic.

Results from the statistical analysis also indicate that the rheumatologists from the eRA group did not comply as well with Drug Toxicity Monitoring Rules as they did with Rules for Changes in Dose/Agent. Moreover, the results show that the eRA group had a significantly poor compliance rate with the recommendations based on Drug Toxicity Monitoring Rules as that seen in the non-eRA group. The findings also may

be explained by the extensive eRA clinic experience with Rules for Changes in Dose/Agent and the Dose Modification Protocol, whereas the formulation of prescriptive Drug Toxicity Monitoring Rules had been overlooked and were formulated during the present project and little clinical experience with these latter rules had accrued. The discrepancy between the considered evidence-based and expert consensus-based Drug Toxicity Monitoring Rules and the variable *ad hoc* responses of rheumatologists to the toxicity scenarios underlines the need for further clinical validation of the rules. The observed low concordance with Drug Toxicity Monitoring Rules was not unexpected as this product of Knowledge Engineering and guideline development proved to be remarkably complex to an extent likely to defy consistent unaided real-time manual application. The analysis identified that both groups had 19% decision revision against the eRA guidelines due to providing additional patient information. In addition, the analysis revealed a variation in applying the drug dosage between the RA management rules and actual practice. These findings further highlight the need of clinical evaluation for the development of CPGs.

9 Summary and Conclusions

The decision-making involved in adjusting treatments for the management of RA is a complicated task for clinicians due to the complexities of response-driven combination DMARD therapy and the need to balance imperatives of adequacy of clinical response with safety considerations in relation to possible drug toxicity. A CDSS has been proposed to integrated up-to-date evidence and therefore to assist clinicians in making better decisions in terms of complying clinical guidelines and mitigating drug toxicity in RA management.

The primary objective of the study was to establish and articulate explicitly the RA management rules in the eRA clinic, as a basis for implementing a knowledge-based CDSS for improved guideline compliance and better RA management. The study hypotheses are (1) the conscientious use of best evidence in clinical decision-making can be achieved through application of Knowledge Acquisition processes in order to facilitate the generation of CPGs, (2) a computer interpretable model can be established for highly complex CPGs, (3) the CDSS guidance concurs with interpretation of the RA management rules for dosage adjustment by clinicians experienced in their application and accepting of the rules, and (4) more complex CPGs are associated with low compliance using manual approach regardless of high guideline acceptance.

During this project, I applied Knowledge Engineering as a technique for the development of the eRA-CDSS. The data and Knowledge Acquisition achieved is a fundamental aspect of this project. During the early stage of the Knowledge Acquisition, I reviewed literature, observed the eRA clinic consultations, consulted the local clinicians and clinic experts, and investigated the eRA clinic database. Studying the clinic database revealed that inconsistency existed in complying the eRA Dose Modification Protocol during the clinic practice, particularly under the circumstances of managing individualised patient toxicity risks. As a result of my insight, the eRA clinic became committed to establishment of more comprehensive RA management rules that addressed this unwanted variability in application.

In order to develop evidence-based clinical guidelines, clinical evidence has to be identified and characterised. Reviewing literature, observing clinic consultations and consulting clinicians played a central role during the development and articulation of the evidence-based RA management rules. These processes helped to synthesize the clinical evidence from the relevant literature and the clinical experts.

During the processes of Knowledge Acquisition, I preformed a comprehensive literature review of MTX toxicity management in RA. I identified the risk factors for MTX toxicity in RA. I also characterised the MTX toxic effects, such as symptoms and abnormal laboratory results. Furthermore, I categorised the identified evidence into evidence categories using the evidence grading methodology defined by Shekelle *et al* [166]. The categorisation helped to identify high grade evidence, with which to underpin clinical guideline development using the best available evidence. In addition, conditional probability, Bayes' theorem and Bayes Net were studied in order to represent the dependence between risk factors, toxicities and toxic effects.

With my assistance, the eRA clinic established the comprehensive RA management rules including Drug Toxicity Monitoring Rules and Rules for Changes in Dose/Agent. The RA management rules have incorporated higher grade evidence identified from the literature. I have also established the framework for MTX toxicity prediction models of hepatic toxicity, haematological toxicity, pulmonary toxicity and gastrointestinal toxicity. I applied Bayes Net for model formation. The models incorporate identified risk factors for MTX toxicity in RA, and clinical effects of MTX toxicity such as symptoms of toxicity and abnormal laboratory results. The development of MTX toxicity prediction models aimed to provide extra decision-making assistance to clinicians in estimating the patient's risks for developing MTX toxicity according to the patient's present risk factors, symptoms, and abnormal laboratory results.

Due to the characteristics of management of a chronic disease such as RA, it is necessary to embrace management rules that feature dynamic state transitions over

time. As a result the RA management rules proved to be highly complex, especially the Drug Toxicity Monitoring Rules. For this reason, computer interpretable models are needed before implementing them into the CDSS. A number of guideline representation models have been developed by the Health Informatics community [170]. Tu et, al. [169] have recommended using Decision Maps to represent static recommendations and using guideline processes to link the individual static recommendations together as a computational model. However, because of the dynamic characteristic of the RA management rules, the transitions between states are unpredictable and there are no straight forward "guideline processes" that can link the static recommendations. The study developed a novel guideline representation model - a dynamic model. The dynamic model describes the dynamic state transitions as a parent-child relationship. The dynamic model includes a node table; each row contains a complete set of children states in relation to each parent state. The dynamic model also includes a decision table which contains the static recommendations of each state. Based on the parent-child relationships, an algorithm was established for computerisation of the rules. The dynamic model ultimately realised electronic implementation of the complex RA management rules.

During the study, I analysed the workflow and data flow of the eRA clinic. I investigated the clinical decision-making process and patient assessment process in detail. I integrated the knowledge models into the above processes. In order to assess the potential impact of incorporating the eRA-CDSS, I also performed the stakeholder analysis.

The preliminary version of the eRA-CDSS was implemented. This prototype captured and implemented the eRA Dose Modification Protocol, Rules for Changes in Dose/Agent, and Drug Toxicity Monitoring Rules. I then conducted a questionnaire-based study in order to test the acceptance of the computerised guideline recommendations by practising rheumatologists; to discern the gaps between the guidelines and practice; and to collect valuable information for developing the CDSS tool with regard to broader clinical acceptability. The questionnaire tested and

analysed the distance and direction between decisions made by clinicians and guideline recommendations generated by the eRA-CDSS.

Statistical analysis showed that (1) the eRA group of rheumatologists had better agreement with the CDSS recommendations compared to the non-eRA group of rheumatologists; (2) rheumatologists in the non-eRA group practised more conservatively compared with the rheumatologists in the eRA clinic (P value = 0.0079); (3) the eRA group had a significantly higher mean compliance rate in scenarios designed to test for adjustment of triple therapy without complicating unwanted effects than the non-eRA group (0.7857 vs. 0.3929, P = 0.0027); (4) both groups had low to moderate compliance rates in scenarios chosen to test responses to out-of-range laboratory results and there was no significant difference in mean compliance rates between the two groups (0.3611 vs. 0.4167, P = 0.7215). This poor concordance underlines the value of computer aided guidance when decisions involve greater complexity; and (5) for both groups, 19% of the decisions relative to the both rules were revised when additional patient information was provided.

The questionnaire validated the hypothesis, which is that the CDSS guidance concurs with interpretation of the RA management rules for dosage adjustment by clinicians familiar with their application, and well accepting the rules. By contrast, the Drug Toxicity Monitoring Rules, which were developed as a considered best practice approach, achieved low compliance rates and no higher concordance by eRA rheumatologists than by those not involved in the eRA clinic. This discrepancy verified the hypothesis, which is that the complexity of the Toxicity Monitoring Rule makes it difficult to apply consistently using manual approach. Hence the delivery of clinical guidelines by CDSS is needed to assist clinical decision-making when the CPGs are well accepted by clinicians, and the complexity of CPGs is high.

Both groups thus had low compliance rates for Drug Toxicity Monitoring Rules, and 19% decision revision when supplied with additional information suggesting that (1) the complexity of the rules reduces compliance, in which case, the CDSS tool can

facilitate this process; and (2) further studies should be carried out to validate the evidence behind the rules and to assess their implementation further.

The overall eRA experience of more than 160 patients, treated according to the Dose Modification Protocol and Rules for Changes in Dose/Agent has not been associated with any serious drug-related toxic events to date. Along with demonstrably more conservative responses of non-eRA rheumatologists, this experience suggests that the rules deliver better disease control without an important increase in serious unwanted events than routine or standard care. The more conservative approach is likely to arise from concerns regarding drug toxicity which may not be well grounded in terms of actual risk. Systematic implementation of the Drug Toxicity Monitoring Rules developed in this project and implementation of a drug toxicity risk assessment tool to identify sub-groups in which a more conservative approach may indeed be appropriate or in whom more intensive toxicity monitoring may be required, should deliver refinements that increase confidence in more intensive application of treatment where appropriate, while managing risk better.

The study has formulated a framework for predicting MTX toxicity. This model holds promise for presenting additional clinical evidence to the clinicians, thereby supporting clinical decisions more completely. However, based on the comprehensive literature review performed during the study, the probability data that quantify the MTX toxicities based on its risk factors or its associated toxic effects were not available. Accordingly neither the Bayes Net model, nor the decision tree model was realised during this project. Nevertheless, the conceptual framework established offers a new mechanism for managing patient risks of drug toxicity; it thereby provides the foundation for future model enhancement and implementation.

In summary, Knowledge Acquisition methodology proved effective in the development and the implementation of a clinically sophisticated CDSS for the management of a serious and highly prevalent rheumatic disease. Complex clinical guidelines were computerised in order to assist clinicians make better decisions for the management of RA. In future risk factors for drug toxicity can be established, and drug

toxicity prediction models can be created using Bayes Net. I believe that the implementation of drug toxicity prediction models can complement the clinical guidelines, thus optimising clinical decision-making for customised patient care.

This study outlines the process of building a knowledge-based CDSS, and addresses questions regarding computerising complex CPGs. The study also acknowledges that an understanding of the issues regarding CPG acceptance is important for effective implementation of a CDSS in a real clinical setting. I am optimistic about the potential impact of the eRA-CDSS on clinical decision-making. Furthermore, because new evidence continually emerges from research and accumulated clinical experience, this CDSS can be updated when and where necessary through knowledge management to incorporate new and compelling evidence as it becomes available.

10 Discussion and Future Directions

In today's healthcare environment, new evidence is continually being published. The availability of updated knowledge is desirable for patients and clinicians. However, determining how to best utilise new knowledge, and thereby improve decision-making in the care of patients is a daunting challenge. In the management of RA, the decision-making involved in adjusting treatment to achieve best outcomes with due regard to benefits and risks is a complex task. Busy clinicians have difficulty incorporating the extensive knowledge and evidence available into the decision-making process, which results in gaps between evidence and practice.

CDSS tools with automatically generated guidelines can positively influence clinicians to comply with guidelines. CDSSs can be integrated into clinical workflow, delivering the right information at the right time in order to assist in clinical decision-making. However, in order to realise an effective and therefore widely accepted CDSS by clinicians, clinical sophistication, workflow integration and guideline validation must all be addressed as these a critical determinants of success.

Gaps between practice and evidence

The use of CPGs has been widely promoted to assist clinicians in making decisions about appropriate management of specific clinical circumstances. CPGs are based on best available evidence and play a role in closing gaps between practice and evidence. However, it has proven difficult to convince clinicians to utilise clinical guidelines in practice as evidenced by the limited impact of guidelines in changing the ways that clinicians practice. Moreover, CPGs are not designed to address every aspect of patient care. They provide generic recommendations that do not take into account variations in individual patients that are needed to address complex clinical scenarios. To provide personalised treatment, clinicians need to incorporate extra knowledge into their decision-making processes. This study established a drug toxicity prediction model to complement standard CPGs. Although the model has not been implemented during project, it provides an alternative way of synthetically integrating clinical evidence into clinical decision-making.

Guideline development

Knowledge acquisition is a critical process during the development of CPGs. An exhaustive systematic review of relevant literature is needed to capture durable and up-to-date evidence. Categorisation of levels of evidence underpins the strength of the recommendations. Clinical expertise can be elicited through consulting/interviewing clinicians. Think-aloud strategies that verbalise their briefs, judgements and decision-making are useful adjuncts to formulation of guidelines. This study reviewed over 150 relevant papers, and intensively engaged the eRA clinicians. These processes led to more comprehensive RA management rules and identified deficiencies in the literature that could be addressed in order to develop management rules further.

Guideline validation

A lack of guideline acceptance is one barrier to applying guidelines in patient care. This study included a questionnaire designed to evaluate congruence between guideline performances as implemented by the CDSS and simulated *ad hoc* clinical decision-making. By conducting the questionnaire, I identified the gaps between the guidelines and the actual practice, which suggested the causes for guideline violation with complexities of decision-making emerging as a candidate factor. The questionnaire identified opportunities for the CDSS to complement CPGs by incorporating extra knowledge to assist clinical decision-making, particularly in the management of out-of-range laboratory safety monitoring data. The study also provided valuable information for future guideline developers to refine, enhance, and develop guidelines.

Work flow integration

Performing a clinical workflow analysis helped to identify opportunities for integration with current clinical practice in order to provide the most direct beneficial effects of a CDSS in the clinic. Understanding clinical decision-making processes was crucial for this integration into the clinical workflow. Mapping knowledge and decision-making points underpins the seamless integration into clinicians' decision-making procedures, which is needed for a clinically acceptable and effective CDSS.

Computer interpretable model development

Over the past decade, adherence to CPGs has become the gold standard for ensuring quality in clinical practice. Researchers and developers have been developing software applications that computerise these guidelines and protocols in order to provide decision support at points of care. However, the complexity of clinical guidelines brings the challenges to implementation. A chronic disease such as RA involves patient state transitions over time. The established RA management rules specify patient conditions and corresponding clinical recommendations for the conditions that take place over time. Furthermore the descendant states of each ancestor state during a state transition are dynamic, and these involve considerable understanding.

This study detailed the construction of a dynamic model with which to interpret complex clinical guideline. Utilising parent-child relationships to represent the dynamic state transitions makes the model distinct from other guideline modelling methodologies. The dynamic model includes a node table; each row contains a complete set of children states in relating to each parent state. The dynamic model also includes a decision table which contains the static recommendations relative to each patient state. A preliminary version of the CDSS has successfully automated the established RA management rules. This established dynamic model can be adopted for modelling clinical guidelines which feature dynamic state transitions, thereby underpinning the electronic implementation of complex CPGs.

A CDSS development processes

A clinically efficient CDSS requires a sophisticated knowledge base. Acquiring the required knowledge for clinical decision-making and representing the knowledge are challenging tasks. I have summarised the processes that I applied in this study as follows:

1. Knowledge acquisition from clinical expertise and best available evidence from relevant literature and research findings

2. Understanding of clinical decision-making processes, and mapping knowledge to the decision-making points in order to integrate knowledge with decision-making processes
3. Establishment of a computer interpretable model for CPGs. The model can address many contingencies of a complex CPG, thereby enhancing compliance with guidelines
4. Identification of fields of Extra knowledge needed to complement the guidelines because the CPGs have limited customisation potential for individuals (atypical patients). An extra knowledge model could be set up to provide evidence-based recommendations in addition to CPGs
5. Exploration of decision theory approaches to assist clinical decision-making, e.g., establishing a Bayes Net model of drug toxicity prediction, which uses known risk factors and toxic effects to project probabilities for occurrence of drug toxicity

Further enhancement

1. MTX toxicity prediction model

One of the major achievements of the study is to have identified and categorised the MTX toxicity risk factors through a comprehensive review of literature. This undertaking examined the risk factors of MTX toxicity in RA. The framework for MTX toxicity prediction models was established by constructing a Bayes Net model utilizing the identified risk factors.

However, the literature review failed to pin down the probability data which quantifies the MTX toxicities based on its risk factors and toxic effects, therefore the MTX toxicity prediction model has not been implemented during the study. Nevertheless, the model construct provides a foundation for future model development and implementation. The lack of probability data in the literature identifies where research is needed to quantify probability with regard to frequencies of drug toxicity that can be used to manage risks of toxicity.

2. Guideline evaluation

Preliminary evaluation of the guidelines as computed by the CDSS yielded positive outcomes with regard to concordance with decisions of the eRA clinic rheumatologists accustomed to applying rules. While the Rules for Changes in Dose/Agent are not without some complexity, the Drug Toxicity Monitoring Rules developed based on my literature review and consultations with clinical experts are far more complex. It was hypothesized that there would be poor concordance with these complex rules as proved to be the case.

A limitation of the study was that the questionnaire had restricted number of patient cases and limited participations. As a consequence, the study was not able to conduct compliance analysis on categorised levels of experience among the participants, or to perform guideline evaluation by case study. For further enhancement, conducting studies to evaluate the developed CDSS on patient outcomes and clinicians' performance will yield further insights into application and effectiveness of the CDSS.

3. Terminology reference

The study did not address any aspects of the standard clinical terminology reference such as SNOMED CT, because it was not in the scope of this project. However, for future development, the study should incorporate the standard terminology reference wherever possible.

4. Data mining

A CDSS has the potential to apply data mining tools to determine the type and frequency of breaches to automated guideline recommendations. Frequency patterns and their associated data can be submitted to clinical experts for interpretation. This information is extremely valuable for the evaluation and improvement of guidelines, and can be used to promote a continuous improvement model in healthcare practice.

Due to a lack of probability data available in the literature, the study failed to extract the probability data that quantifies the MTX toxicity presence according to the patient's risk factors and existing drug toxic effects. However, through integration with special data mining tools, a CDSS can help to collect the probability data from the

users (clinicians). These data can potentially feed Bayes Net model and realise the drug toxicity prediction model.

What this study adds to the topic?

Unlike most CDSS projects which implemented already available clinical guides, this study adopted a novel approach of Knowledge Engineering into the development of a CDSS for assisting decision-making in the management of RA. The Knowledge Acquisition processes through which the evidence-based RA management rules have been established have more general utility.

Significant contributions to knowledge are summarised as follows:

1. The Knowledge Acquisition processes embraced by the study facilitated not only the synthesis of high quality clinical evidence for RA management, but also underpin the establishment of the RA management guideline. Clinical evidence is the key ingredient which forms the knowledge base of a CDSS. Identifying clinical evidence through comprehensive literature review was an important aspect of the study. This study also interactively engaged the local clinical experts. A think-aloud strategy was used to elicit clinical expertise. Encouraging clinicians to articulate their premises (knowledge, beliefs) and inferences proved useful in formulating treatment rules.

2. The establishment of the computer interpretable model underpinned the success of the automation of guidance during the CDSS development. The computer interpretable model (dynamic model) facilitated the implementation of highly complex CPGs. This model is unique compared to other guideline models, because it models unpredictable state transitions during the RA management pathway. State transitions are a typical characteristic of chronic disease management and accordingly the model architecture has more general utility.

3. The questionnaire explored the level of concordance between guidelines and rheumatologists responding to care scenarios. The gaps between guideline recommendations and physician responses allowed a number of inferences to be

made. These included an endorsement of the effectiveness of the computational model as evidenced by better concordance by clinicians familiar with Rules for Changes in Dose/Agent. This analysis also underlined the potential importance of computer aided guidance in the application of highly complex rule as evidenced by poor concordance with the Drug Toxicity Monitoring Rules, including physicians familiar with the eRA approach.

4. Drug toxicity prediction model was another unique modelling approach of the study. Exhaustive literature review identified a complete list of MTX toxicity risk factors in RA, which formed the knowledge base of the MTX toxicity prediction model. However due to the lack of required conditional probability data from the literature, the drug toxicity prediction model has not yet to be realised. Therefore the preliminary version of the eRA-CDSS only implemented the clinical guideline models. Nevertheless, this study takes tangible steps toward the ultimate goal of developing a specifically designed, clinically sophisticated Knowledge-based CDSS with the feature of computerising highly complex CPGs that deliver evidence-based recommendations.

With today's aging population, the high prevalence of chronic diseases and increased changes in the use of medications, clinical decision-making is becoming more complex. In order to make better decisions in increasingly complex circumstances, we need sophisticated systems to assist with decision-making. CDSSs were introduced more than two decades ago to assist with clinical decision-making, yet more effort is required to optimise systems. I believe that in addition to 'workflow', 'clinical sophistication' is also a key to the development of effective CDSSs, while Knowledge Acquisition is fundamental to the process of system development.

Medical practice inevitably will diverge to some extent from knowledge and new evidence. Substantial work is needed to realise the full potential of CDSSs to close the 'evidence-practice gap' through the delivery of knowledge and guidance to the clinician at point of care. As new evidence continually arises from research, including that arising from the outcome data collected by CDSSs, and accumulated clinical

experience, the design of CDSSs not only needs to allow for an analysis of clinical inputs, but also needs to be amenable to system refinements based on an analysis of system performance and emergent scientific information.

Looking to the future, there is another application for CDSSs, which has implications for quality of care and also for the rising cost of new treatments. This application increases the use of CDSS guidance to provide a background of response-contingent best practice care with consistent actions in response to out of range blood results and drug intolerances, during the evaluation of novel therapeutic additions to usual combination therapies for chronic diseases. This application should displace prevailing comparison between new drugs and minimum acceptable comparators which inflate the apparent value of new treatments. The resulting perceptions of efficacy then became translated into high prices based on inappropriately flattering cost-benefit analyses. Thus CDSSs should have a place both in the better delivery of established management strategies and in the evaluation of novel treatments.

Appendices

Study Timetable

Time Frame	Events
September 2004 – December 2005	1. Reviewing literature on RA management 2. Investigating the eRA clinic database
January 2005 – March 2005	1. Reviewing literature on CDSSs 2. Observing the eRA clinic consultation 3. Analysing clinical protocol compliance (Dose Modification Protocol) 4. Drafting research proposal
April 2005 – June 2005	1. Analysing clinical workflow 2. Performing stakeholder analysis 3. Analysing clinical decision-making process
July 2005 – August 2005	1. Reviewing literature on MTX toxicity risk factors in RA 2. Consulting local clinical experts for clinical expertise in managing RA
September 2005 – December 2005	1. RA management rule development 2. Establishing Drug Toxicity Monitoring Rules 3. Establishing Rules for Changes in Dose/Agent
January 2006 – March 2006	1. Reviewing literature on clinical guideline modelling 2. Analysing the complex RA management Rules (rule break down)
April 2006 – June 2006	Establishing computer interpretable guideline model – a dynamic model
July 2006 – August 2006	1. Reviewing literature on Bayes' Theorem and Bayes Net 2. Developing MTX toxicity prediction model
September 2006 – December 2006	1. On leave 2. CDSS implementation (Alcidion corporation)
January 2007 – March 2007	1. Questionnaire study 2. Reviewing patient case note for case data 3. Drafting questionnaire and recruiting participants
April 2007 – June 2007	1. Distributing Questionnaire 2. Collecting, analysing and reporting questionnaire data
July 2007- December 2007	Thesis writing

Questionnaire Cover Letter

Dear Professor/Doctor:

We are asking you to assist in a research project to evaluate the early Rheumatoid Arthritis Clinical Decision Support System (eRA-CDSS). The CDSS automates comprehensive ERA clinical rules, generates recommended drug regimen, dosage and patient monitor plan. The purpose of this evaluation is to ensure wide applicability for the future use of the CDSS in the ERA Clinic or in other clinic settings.

Along with this letter is a questionnaire which includes sixteen patient cases. We ask that you use the clinical information provided to make a decision as to whether treatment should change and if so how. Completion of the questionnaire enclosed will enable us to evaluate the CDSS tool with regard to broader clinical acceptability. The cases are real case abstracts, which have been carefully chosen from the ERA Clinic database as they are suitable for testing our clinical decision rules. Each case abstract has two copies; one copy includes minimum CDSS input, the other copy provides extra patient information. If you choose to participate in our questionnaire, please respond to both copies of each case, then move on to next case. Your responses will not be identified with you in any way and you will not be named in any report. In other words, your responses will be treated in a very confidential manner. Only summarized data will be included in a formal report.

This questionnaire should take you about 45 minutes to complete. We appreciate your time and effort towards this study and we would kindly request you return it to Ning Pan by 13th April 2007. If you have any questions about the questionnaire, you may contact Ning at 82225762 or email to ning.pan@adelaide.edu.au.

Sincerely,

Ning Pan
(PhD student
Health Informatics Unit
The University of Adelaide)

Dr Susanna Proudman
Prof. Les Cleland
(Royal Adelaide Hospital)

Questionnaire Sample

UR: 1183623 **DOB: 6 Feb 1961** **SEX: Female**

Age: 45 **Weight: 54.9kg**

Patient Current Medications

- methotrexate 10 mg orally per week
- folic acid 0.5 mg orally daily
- sulfasalazine EN 1.0 G orally bd
- hydroxychloroquine 400 mg orally daily

Clinical Information

Duration of the therapy:	6 weeks
Tender Joint Count:	8
Swollen Joint Count:	2
Patient pain:	20
Morning stiffness:	0 minute
Fatigue:	25
ESR:	26
CRP:	1.1

Patient Remarkable Symptoms

Patient GI side effects: Nil

Laboratory Results

	Latest Lab	**Prior Lab**
neutrophils (1.80-7.50)	4.73	4.8
ALT (0-55)	34	27
AST (0-45)	-	26
creatinine (50-120)	63	67
creatinine Clearance	(84.4752)	

Physician's Response Detail (Please use block letters)

Need dose modification?

Yes ☐

No ☐

If Yes

Increase ☐ _____ dose _____

Reduce ☐ _____ dose _____

Hold ☐ _____

Restart ☐ _____ dose _____

Stop (can not resume) ☐ _____

Consider adding any new medication?

_____

Patient monitor plan

Repeat lab test in _____ weeks

See patient in _____ weeks

Questionnaire Sample (with extra patient information)

UR:	**1183623**	**DOB:**	**6 Feb 1961**	**SEX:**	**Female**
Age:	**45**	**Weight:**	**54.9kg**		

Patient Current Medications

- paracetamol 500 mg tds
- glucosamine
- vitamins
- **methotrexate 10 mg orally per week Saturday night (began 30/8/06)**
- folic acid 0.5 mg orally daily
- **sulfasalazine EN 1.0 G orally bd (began 30/8/06)**
- **hydroxychloroquine 400 mg orally daily (began 30/8/06)**

Patient Remarkable Symptoms & Other Patient Info

Patient GI side effects: Nil

Clinical Information

	Current Visit	**Prior Visit**
Duration of the therapy	6 weeks	3 weeks
Tender Joint Count	8	13
Swollen Joint Count	2	6
Patient pain	20	24
Morning stiffness	0 minute	60 minutes
Fatigue	25	37
ESR	26	46
CRP	1.1	6.6
Blood Pressure	120/70	110/65

Laboratory Results

	Latest Lab	**Prior Lab**
neutrophils (1.80-7.50)	4.73	4.8
ALT (0-55)	34	27
AST (0-45)	-	26
Haemoglobin (135-175)	115	113
WCC (4.00-11.0)	7.46	7.5
Monocyte (0.20-0.80)	0.33	0.27
Lymphocyte (1.00-3.50)	2.29	2.29
MCV (80.0-98.0)	65.9	66.2
Platelet (150-400)	223	257
creatinine (50-120)	63	67
creatinine Clearance	(84.4752)	

Physician's response detail (Please use block letters)

Need dose modification?

Yes □

No □

If Yes

Increase □ _____ dose _____

Reduce □ _____ dose _____

Hold □ _____

Restart □ _____ dose _____

Stop (can not resume) □ _____

Consider adding any new medication?

_____

Patient monitor plan

Repeat lab test in _____ weeks

See patient in _____ weeks

Tables of MTX Toxicity Risk Factors

Overall MTX Toxicity Risk Factors

Reference	Specific Patient Group / Sample Size	Data Collection Duration	Study Type	Variables	Result	Analytical Method	Identified Risk Factor
Rheumatoid Arthritis Clinical Trial Archive Group [124], 1995	496 patients from 11 placebo controlled and comparative MTX clinical trials; 341(69%) patients less than 60 years old		A meta-analysis	age, renal impairment	Lower Creat CL at baseline assessment is associated with higher rates of overall toxicity (P=0.027); Odds Ratio for severe toxicity and respiratory toxicity were increased from 3 to 6.9 times in those with renal impairment ; Patients in older age group (65-69, >=70) were not at higher risk of toxicity from MTX	Multiple regression analysis, logistic regression analysis	Impaired renal function
Mielants, H., et al., [112], 1991	92 RA patients with MTX 7.5mg/week orally (renal function was normal at baseline);		Open prospective study		2 patients had a fatal outcome because of an unexpected renal deterioration	Not recorded	Impaired renal function

	Mean age of 58 with range from 30 to 81 years						
McKendry, R.J. et al., [111], 1993	144 RA patients; Sub group: 50 patients with adverse reaction and duration of follow up matched controls	13 years (1977-1990)	Retrospective survey	age, sex, renal function, concurrent NSAID and ASA	No significant different between groups with respect to the variables; Discontinuation of therapy due to a major adverse effect was age related	Case control method and logistic regression analysis	Advance age
Buchbinder, R., et al., [113], 1993	587 RA patients	Up to June 1986	Retrospective review	age	Advanced age (>=65) was a significant predictor of drug termination due to toxicity (P<0.001)	Life table analysis	Advanced age (>= 65)
Wolfe, F. et al., [122], 1991	235 RA patients; 184 patients aged over 65 (>65); 51 patients less than 65 (<= 65)	June, 1976 to January, 1990	Retrospective review	age	More gastrointestinal complaints and more pulmonary complaints in older age group	χ^2 statistic; Wilcoxon rank sum test	Advanced age (>65)
Kent, P.D. et al., [143], 2004	481 RA patients including 334 female (69%)	1991-2002	Retrospective cohort study		Lack of folate (P<0.001) and increased BMI (P<0.03) were associate with permanent discontinuation of MTX; Hypoalbuminemia was associate with temporarily	Wilcoxon rank sum test and linear regression analysis; Multivariate	Lack of folate, untreated hyperlipidemia, increased BMI were the risk factors for transaminase

					withdrawal of MTX; Univariate analysis: Lack of folate supplementation (P<0.001), untreated hyperlipidemia (P<0.02), increased creatinine (P<0.03) and male sex (P<0.04) were the risk factors for increased abnormal AST; Multivariate analysis: Lack of folate and untreated hyperlipidemia	linear regression analysis; Pearson χ^2 test	elevation; Hypoalbuminemia was a risk factor for thrombocytopenia
Hoekstra, M., et al., [126], 2003	411 RA patient; Folate supplementation group: (n = 274); Placebo group: (n = 137)	48 week	A randomise clinical trial		Lack of folate (P<0.001), High BMI (P=0.02) were associated with hepatotoxicity; Prior GI events (P=0.03) were associated with GI toxicity; Hepatotoxicity and GI toxicity were the main reasons of withdrawal	Univariate analysis; Multivariate analysis	Lack of folate, high BMI were the risk factors for hepatotoxicity; Prior GI events was the risk factors for GI toxicity
Morgan, S.L., et al., [125], 1990	32 patients were included in trial of folic acid supplementation during low-dose MTX		A 24 weeks, placebo-controlled, double-blind, trial		Folate supplement group had significant lower toxicity scores than placebo group (P=0.027)	student's *t*-test, liner regression model	Lack of folate supplementation is a risk factor for MTX toxicity

	therapy; 16 patients in folate supplement group (folate 1mg/day) and 16 patients in placebo group						
Ortiz, Z., et al., [128], 1998	7 trials (307 patients); 147 were treated with folate supplementation (67 with folic, 80 with folinic acid)		A systematic review	Liver enzyme could not be evaluated because of missing data	A 79% reduction in mucosal and GI side effects was observed for folic acid group (OR=0.21); A 42% reduction for folinic acid	Multivariate analysis; χ^2 test	Lack of folate supplementation is a risk factor for MTX mucosal and GI toxicity
van Ede, A.E., et al., [127], 2001	A total of 434 RA patients were included in the study to compare the effect of folic or folinic acid supplementation on MTX toxicity; 411 were included in the ITT population: 137 in placebo group, 133 in the folic acid group, and 141 in the		A 48 weeks randomized, double-blind, placebo-controlled trial		Toxicity-related MTX discontinuation occurred in 38% of the placebo group, 17% of the folic acid group and 12%of the folinic acid group; There was a significant difference between placebo group and folate supplementation group in incidence of elevated liver enzyme	χ^2 test, student's *t*-test, liner models, log rank test, and Wilcoxon's tests	Lack of folate supplementation is a risk factor for liver enzyme elevation

	folinic acid group; Folic acid: 1mg/day folinic acid: 2.5mg/week Initial MTX: 7.5mg/week (can be allowed up to 25mg/week, folate dosage were doubled once MTX reached 15mg/week)						

MTX Haematological Risk Factors

Reference	Specific Patient Group / Sample Size	Data Collection Duration	Study Type	Variable	Result	Analysis Method	Identified Risk Factor
al-Awadhi, A. et al, [152], 1993	15 cases of pancytopenia(12 RA, 2 PsA, 1 psoriasis); 15 duration of MTX therapy matched controls; 2nd age and sex matched controls (No folate supplementation)	1981-1991	Case-control	dose, age, concomitant medications, renal function and MCV	A MTX therapy duration matched controls shows significant difference with respect to age, renal function and MVC; Pancytopenia group had more advanced age, impaired renal function and elevated MCV; A 2nd age and sex match control shows BUN and creatinine were significantly elevated in pancytopenia group	Paired student's *t*-tests and χ^2 statistic	Renal function, MCV, advanced age
Weinblatt, M.E. et al, [153], 1989	23 RA patients receiving low-dose MTX, 6 patients developed hematologic toxicity		Retrospective analysis	MCV	MCV of the patients who developed toxicity was significantly higher than those without toxicity ($P<0.02$); Elevated MCV was associated with an increased probability of developing toxicity with time ($P<0.005$)	Student's *t*-test and Mann-Whitney U test	MCV
Gutierrez-	Total of 70 patients	15 years	Literature	renal impairment,		Not	renal impairment,

Urena, S., et al. [156], 1996	with pancytopenia (68 reported in literature and 2 from own experience)	(1980-1995)	review + 2 cases report	hypoalbuminemia, concurrent infection, concomitant medication		recorded	concomitant infection, concomitant therapy (including NSAIDs, trimethoprim /sulfamethoxazole), hypoalbuminemia
Maricic, M. et al, [155], 1986	47 years old white woman with RA treated with MTX12.5mg/week		Case report		Developed megaloblastic pancytopenia shortly after trimethoprim/sulfamethoxazole was added to the regimen		MTX treatment with trimethoprim /sulfamethoxazole

MTX Hepatotoxicity Risk Factors

Reference	Specific Patient Group/Sample Size	Study Type	Patient Characteristics	Result	Analysis Method	Identified Risk Factor
Shergy, W.J., et al., [141], 1988	Total 538 MTX treated Patients who underwent liver biopsy from Jan.1979 to Jan.1988, including 210 RA patients with 6 Grade III liver biopsies	Retrospective study	6 patients with RA and Grande III liver biopsies: Sex (M/F): 1/5 Mean age: 59 (50-68) Mean length of therapy:32month(25-48) MTX: (7.5mg-15mg/week)	Diabetes mellitus: 3/6 Obesity: 5/6 Renal insufficiency: 0/6 Alcohol usage: 1/6 Elevated LFT results: 1/6 Declining albumin: 0/6	Tabular presentation of data; Simple descriptive statistics	Diabetes, obesity
Kremer, J.M. et al, [139], 1989	29 MTX treated RA patients (27 patients had follow up biopsies)	A prospective study with baseline and sequential biopsy samples	In 27 patients Sex (M/F): 7/20 Mean age: 50.4±14.1(22-77)	A worsening hepatic histology reflecting by an increase in the mean histological grade over total of six years of MTX therapy; There was a significant association between alcohol assumption and increase in biopsy grade, Increased body weight and fibrosis;	Univariate paired t-test, Signed rank test, multivariate logistic regression analysis	Alcohol, obesity, dose, duration, elevated liver enzymes

				Total duration of MTX therapy was significantly longer in patient with grade IV biopsy than those not; Total cumulative MTX dose was correlated with fibrosis development; Elevated liver enzyme is correlated with liver histological deterioration; There was a significant association between age and the numbers of abnormal AST values		
Whiting-O'Keefe, Q.E. et al, [140], 1991	A total of 636 patients including 334 RA patients) from 15 studies	A meta-analysis		Patients who were heavy drinker (at lease 100g alcohol per week) were more likely to show histological progression and advanced changes; Liver histological progression was correlated with the cumulative dose of MTX.	Linear regression analysis; Multivariate analysis	Alcohol, dose
Walker, A.M., et al.,	24 cases of cirrhosis and liver failure with positive liver	Case-control study		Age at first MTX use and time since initiation of MTX	tabular analysis,	Age, dose and duration, elevated

[144], 1993	biopsy were identified by rheumatologists from 16600 RA patients receiving MTX for 5 years or more. 39 sex, race and treatment history matched controls were found for 16 cases; 8 cases had no matched controls.			therapy were the strongest predictor of liver failure and cirrhosis; AST and serum albumin discriminated well between cases and controls (creatinine are in normal range for cases and controls)	multivariate analysis	liver enzyme, hypoalbuminemia
Clegg, D.O., et al., [116], 1989	A 38 years old woman with 12 years RA receiving MTX for 4 years+ (started with 7.5mg/week, increased to 15mg/week)	Case report		Biopsy revealed chronic active hepatitis which was not found on biopsy 2 years earlier. The patient developed serious liver failure (ascites) while continuing MTX treatment. However the patient recovered after the MTX therapy was discontinued		MTX-related hepatic
Kujala, G.A., et al., [117], 1990	58-year-old white woman with 22 years RA	Case report		A liver biopsy revealed chronic hepatitis with bridging fibrosis and piecemeal necrosis. Upon discontinuation of MTX, the patient's ascites resolved		MTX-related hepatic

MTX Pulmonary Toxicity Risk Factors

Reference	Specific Patient Group / Sample Size	Study Type	Result	Analysis Method	Identified Risk Factor
Searles, G. et al, [130], 1987	reported 4 cases and reviewed 6 published cases in the literature	Case reports and a review of the literature	Clinical features of 10 cases: all had dyspnea and most of them had cough and fever; Profile of possible risk factor: six patients had a history of smoking and four patients had pre-existing pulmonary diseases	Not recorded	Smoking, pre-existing pulmonary diseases
Golden, M.R., et al., [132], 1995	93 women and 32 men with RA treated with MTX for any period of time between Jan. 1980 and Jul. 1989	case-review study	MTX pneumonitis occurred in 4 of 77 (5.2%) patients without pre-existing lung disease and 5 of 29 (17.2%) patients with pre-existing lung disease (P=0.0610, Fisher's exact test). There are no differences between those developing pneumonitis cases and those not developing pneumonitis in age, sex, accumulation of MTX dose and duration of therapy. The clinical characteristics of the 9 MTX pneumonitis patients are coughing, fever and dyspnea	Univariate analysis; Multivariate analysis	Pre-existing pulmonary disease
Carroll, G.J., et al., [107], 1994	12 patients with MTX pneumonitis were compared with 24 age/sex matched controls	case-control study	A shorter duration of MTX treatment and a higher incidence of pre-existing lung disease were observed in MTX pneumonitis cases, but no significant statistical differences. Two groups have no difference in smoking, RA duration, MTX dosage, and creatinine clearance	Not recorded	pre-existing lung disease

Alarçon, G.S., et al., [131], 1997	29 patients with MTX pneumonitis from 1981 to 1993 were compared with 82 controls	case-control study	Case-patients were more likely be advanced in age, smoker, with rheumatoid pleuropulmonary involvement, with previous use of antirheumatic drugs and low serum albumin	logistic regression model	Advanced age, smoking, rheumatoid pleuropulmonary involvement, previous use of antirheumatic drugs and low serum albumin
Kremer, J.M., et al., [136], 1997	27 RA patients with MTX lung injury and 2 with probable MTX lung injury between 1981 and 1993 were identified	Retrospective combined cohort review and extracted from the English medical literature	Symptoms are normally present for several weeks before diagnosis. Earlier recognition and drug withdrawal may avoid serious outcomes	Not recorded	Clinical features including shortness of breath, cough and fever, sputum production, tachypnea, rales on examination

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