Knowledge Engineering
Complex Decision Support System
in Managing Rheumatoid Arthritis

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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

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

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<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>ACR</td>
<td>American College of Rheumatology</td>
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<tr>
<td>ADE</td>
<td>Adverse Drug Event</td>
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<td>ADR</td>
<td>Adverse Drug Reaction</td>
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<tr>
<td>ALT</td>
<td>Alanine Transferase</td>
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<tr>
<td>Arava</td>
<td>Leflunomide</td>
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<td>AST</td>
<td>Aspartate Transaminase</td>
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<td>AZA</td>
<td>Azathioprine</td>
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<tr>
<td>CBE</td>
<td>Complete Blood Examinations</td>
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<td>CDSS</td>
<td>Clinical Decision Support System</td>
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<tr>
<td>CPG</td>
<td>Clinical Practice Guideline</td>
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<tr>
<td>CPOE</td>
<td>Computerised Physician Order Entry</td>
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<td>CPR</td>
<td>Computer-based Patient Record</td>
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<td>Creat Cl</td>
<td>Creatinine Clearance</td>
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<td>CRP</td>
<td>C-reactive Protein</td>
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<tr>
<td>DAS</td>
<td>Disease Activity Score</td>
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<td>DMARDs</td>
<td>Disease Modifying Anti-Rheumatic Drugs</td>
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<tr>
<td>EBM</td>
<td>Evidence-based Medicine</td>
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<tr>
<td>EMS</td>
<td>Morning Stiffness</td>
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<td>ESR</td>
<td>Erythrocyte Sedimentation Rate</td>
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<td>eRA</td>
<td>early Rheumatoid Arthritis</td>
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<tr>
<td>eRA-CDSS</td>
<td>early Rheumatoid Arthritis-Clinical Decision Support System</td>
</tr>
<tr>
<td>GI</td>
<td>Gastrointestinal</td>
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<tr>
<td>Gold</td>
<td>Intramuscular Myocrisin</td>
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<tr>
<td>GUI</td>
<td>Graphic User Interface</td>
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<tr>
<td>HCQ</td>
<td>Hydroxychloroquine</td>
</tr>
<tr>
<td>IM</td>
<td>Intramuscular</td>
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<tr>
<td>LFT</td>
<td>Liver Function Tests</td>
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<tr>
<td>MCV</td>
<td>Mean Corpuscular Volume</td>
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<tr>
<td>MeSH</td>
<td>Medical Subject Headings</td>
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<tr>
<td>Acronym</td>
<td>Definition</td>
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<tr>
<td>mHAQ</td>
<td>modified Health Assessment Questionnaire</td>
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<tr>
<td>MTX</td>
<td>Methotrexate</td>
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<tr>
<td>Neoral</td>
<td>Cyclosporine A</td>
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<td>NSAIDS</td>
<td>Non-Steroidal Anti-Inflammatory Drugs</td>
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<tr>
<td>RA</td>
<td>Rheumatoid Arthritis</td>
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<td>RAH</td>
<td>Royal Adelaide Hospital</td>
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<td>RAQoL</td>
<td>Rheumatoid Arthritis Quality of Life Questionnaire</td>
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<tr>
<td>SDLC</td>
<td>Software Development Life Cycle</td>
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<tr>
<td>SF36</td>
<td>36-item Short Form Health Survey</td>
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<td>SOA</td>
<td>Service Oriented Architecture</td>
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<tr>
<td>SSA</td>
<td>Sulfasalazine</td>
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<tr>
<td>TNF</td>
<td>Tumour Necrosis Factor</td>
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<tr>
<td>UML</td>
<td>Unified Modelling Language</td>
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<tr>
<td>UNL</td>
<td>Upper Normal Limit</td>
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<tr>
<td>URTI</td>
<td>Upper Respiratory Tract Infection</td>
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<tr>
<td>UTI</td>
<td>Urinary Tract Infection</td>
</tr>
<tr>
<td>VAS</td>
<td>Visual Analogue Scale</td>
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<tr>
<td>WHO</td>
<td>World Health Organisation</td>
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