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A Web-Based System for Determining Drug Dosing Levels in Kidney Impairment

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Head of Discipline: Dr. Michael Madden

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University Hospital Galway, Ireland (UHG) uses a hybrid system to maintain patient records. Some wards have an electronic health record (EHR), while others are still dependent on paper records. The continued use of paper records represents a significant risk in relation to prescribing and managing certain drugs, as calculating the correct dosage involves error prone, multistep, algebraic calculations. This is a greater risk for patients more susceptible to drug toxicity such as premature babies, children and adults with kidney or cancer disease.

Although drug dosage calculations have been automated for some time, the software solutions do not necessarily comply with local hospital guidelines, which undergo constant change. They are often stand-alone calculators that do not provide any additional feedback to clinicians. The quality of such calculators varies widely and transparency of the validation process is close to non-existent. In addition, changes in regulatory advice and the introduction of new drugs dictate that these systems must be constantly updated. This research is the result of a collaborative project with UHG and an effort to address the above issues. It involved a number of important UHG stakeholders, mainly the lead clinical pharmacist and members of the antimicrobial management team. This research resulted in the development of a tool that allows a trained clinical pharmacist to define and validate complex drug dosage regimes. These are then available to clinicians for drug dosage calculations, via a range of platforms such as a mobile phone or desktop PC. The system can be populated by a trained clinical pharmacist without requiring any changes in coding. The software can also report the data to doctors on their ward rounds, so that at-risk patients may be easily identified.
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Table 1. Mobile Technology Generations

List of Terms

3G – Third Generation in Mobile Communication
CDMA – Code Division Multiple Access
CPR - Computer-based Patient Record
CrCl - Creatinine Clearance
DMR - Digital Medical Record
DTD – Document Type Definition
EDGE – Enhance Data rates for GSM Evolution
EAHP – European Association of Hospital Pharmacists
eGFR - Estimated Glomerular Filtration Rate
EHR – Electronic Healthcare Record
EJB – Enterprise JavaBeans
EMR - Electronic Medical Record
EPR - Electronic Patient Record
FDMA – Frequency Division Multiple Access
HIT – Healthcare Information Technology
HPAI – Hospital Pharmacists Association of Ireland
HSPA – High Speed Packet Access
HTML – Hypertext Markup Language
HTTP - HyperText Transfer Protocol
IaaS - Infrastructure as a Service
IMT – International Mobile Telecommunications
IOM - Institute of Medicine
IT – Information Technology
J2SE – Java Platform 2 Standard Edition
JAXB – Java API for XML Binding
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tr>
<td>JAXP</td>
<td>Java API for XML Parsing</td>
</tr>
<tr>
<td>JDBC</td>
<td>Java DataBase Connectivity</td>
</tr>
<tr>
<td>JEE</td>
<td>Java Platform Enterprise Edition</td>
</tr>
<tr>
<td>JPA</td>
<td>Java Persistence API</td>
</tr>
<tr>
<td>JSF</td>
<td>Java Server Faces</td>
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<tr>
<td>JSP</td>
<td>Java Server Pages</td>
</tr>
<tr>
<td>JTA</td>
<td>Java Transaction API</td>
</tr>
<tr>
<td>LAN</td>
<td>Local Area Network</td>
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<tr>
<td>LTE</td>
<td>Long Term Evolution</td>
</tr>
<tr>
<td>MVC</td>
<td>Model View Control</td>
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<td>NCC MERP</td>
<td>National Coordinating Council for Medication Error Reporting and Preventing</td>
</tr>
<tr>
<td>NUIG</td>
<td>National University of Ireland, Galway</td>
</tr>
<tr>
<td>ORM</td>
<td>Object Relational Mapping</td>
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<tr>
<td>PaaS</td>
<td>Platform as a Service</td>
</tr>
<tr>
<td>PC</td>
<td>Personal Computer</td>
</tr>
<tr>
<td>PDA</td>
<td>Personal Digital Assistant</td>
</tr>
<tr>
<td>PHR</td>
<td>Personal Health Record</td>
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<tr>
<td>PMRI</td>
<td>Patient Medical Record Information</td>
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<tr>
<td>POJO</td>
<td>Plain Old Java Objects</td>
</tr>
<tr>
<td>SaaS</td>
<td>Software as a Service</td>
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<tr>
<td>SAX</td>
<td>Simple API for XML parsing</td>
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<tr>
<td>SQUID</td>
<td>System for Quality Use of Drugs</td>
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<tr>
<td>TDMA</td>
<td>Time Division Multiple Access</td>
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<tr>
<td>UHG</td>
<td>University Hospital Galway</td>
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<tr>
<td>UMTS</td>
<td>Universal Mobile Telecommunications System</td>
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<tr>
<td>URL</td>
<td>Uniform Resource Locator</td>
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<tr>
<td>WAN</td>
<td>Wide Area Network</td>
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<tr>
<td>WCDMA</td>
<td>Wideband CDMA</td>
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<tr>
<td>XML</td>
<td>Extended Markup Language</td>
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I would like to express my sincere gratitude to my supervisor Dr. Michael Schukat and Mr Peter Kidd for their valuable advice and patience.

I would like to extend my thanks to all my loving friends, family members, lab mates and colleagues for their help and support.
1. Introduction

Mr Peter Kidd, a lead clinical pharmacist of 20 years, contacted Dr Michael Schukat of the IT Department in National University of Ireland, Galway (NUIG) in September 2009, with a view to developing software capable of calculating the doses for several drugs that depend on the kidney for elimination. The concept was not confined to drugs affected by the kidney; however this was the team’s first priority. I was assigned to this project as part of my 2nd year M.Sc. (SD&D) project. This project resulted in an Adobe based “stand-alone” drug calculator. This calculator captures the input parameters such as age, sex, weight, height and serum creatinine and advises the appropriate doses of gentamicin drug for patients.

During this time I discovered that there was a lot of scope in this area for potential software research and development. In September 2010, I decided to research further into medication errors, especially with respect to patients with kidney impairment.

The result of this work is presented in this thesis.

What are Medication Errors?

The National Coordinating Council for Medication Error Reporting and Preventing (NCC MERP) [1] define a medication error as:

“A medication error is any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems, including prescribing; order communication; product labelling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.”

Medication errors are not only harmful but also expensive. For example, in the US the annual number of deaths caused due to medication errors, is greater than the number of deaths caused by highway accidents, breast cancer and AIDS combined
According to the Institute of Medicine (IOM), the ‘To Err is Human’ report in 1999 highlighted that between 44,000 and 98,000 people die in US hospitals each year due to medication errors [3]. The US survey results of HealthGrades (HealthGrades 2004, 2007, 2008, 2009) show that the number of deaths due to medication errors, has increased steeply since the IOM report. Some of the findings of the HealthGrades survey [4] [5] [6] are:

1. From 2000 to 2002, an average of 195,000 people died annually due to potentially preventable in-hospital medical errors.
2. From 2003 to 2005, the combined number of deaths was 247,662. The cost incurred over this period due to medication errors was approximately $8.6 billion.
3. From 2004 to 2006, the associated cost increased to $8.8 billion, and the total number of deaths rose to 238,337.

The most common type of medication errors are:

1. Prescribing erroneous medications and or doses of medications
2. Inappropriate monitoring of laboratory parameters
3. Filing system errors
4. Dispensing the wrong medications
5. Failing to promptly respond to abnormal laboratory test results

1.1. Research Area

Insufficient knowledge of drug therapy and dosage calculations, improper evaluation of patient characteristics and respective drug dosage formulations, are key causal factors for medication errors while prescribing a drug [7]. Excessive doses may produce toxic effects, while insufficient doses may fail to treat the patient. A few drugs have a small margin between the toxicity and treatment failure. These drugs are called low therapeutic index drugs [8]. The therapeutic index is the ratio of the maximum accepted dose to the minimum curative dose. Patients with kidney impairment are particularly at risk of toxicity or under dosing. The types of patients most susceptible to ‘wrong kidney dosing’ include adults with chronic kidney disease,
cancer or critical illness, as well as newborn babies and children with kidney impairment [9].

The main reasons for wrong dosage calculation in kidney impairment are described in chapter three.

One frequent example is the dosing error associated with gentamicin, a potent antibiotic capable of causing kidney failure if incorrectly used [10]. Whilst low-technology strategies such as paper-based dosing algorithms are available, physicians need to calculate the dose using a complex, multi-step process. Although any qualified physician is capable of carrying out this process, the skill must be learned correctly and is time consuming, which may be difficult due to time pressure on junior doctors. Taking this challenge into account, it was concluded that an automation of dosage calculation and communication of this dose to a specialist antimicrobial team, would result in more patients receiving the correct dose of medication.

Such an automation system would have the following clinical requirements:

1. **Accuracy / input validation** - In particular, all user inputs must be validated for correctness / plausibility, i.e. an incorrect patient weight will result in an incorrect and possibly lethal dosage.

2. **Transparency** - The end user of this system should have the complete knowledge of the backend protocols and algorithms used while calculating the dosages, so they may fully trust the system.

3. **Accessibility** - This system must be available on multi-platforms, such as mobile phones, PDAs and computers, so that the user can access it anytime and anywhere.

4. **Security** - For the confidentiality of patient and clinician information, all the information stored in this system should be stored securely.

5. **Workflow integration** - Clinical pharmacists oversee and manage drug dosage-related activities. In particular, they need to validate and sign-off on any new dosage calculation formulas. For example, a web-based gentamicin
calculator offered by some organisations would not meet a pharmacist’s standard.

6. Adaptability to new dosage formulas - Day to day as new drugs are coming out in the market, this system should have the ability to incorporate new drugs in into the software.

Integrated clinical EHR systems, discussed in more detail in chapter two, provide a suitable platform, in principle, to implement such a framework. However, discussions with clinicians from UHG showed that the EHR route is not necessarily suitable for the implementation of such a system. The main reasons for this are as follow:

- EHR are not widely deployed. These are some of the statistics of the deployment of EHR worldwide [12]:
  1. Less than 2% of US hospitals have a comprehensive EHR system.
  2. 8 to 12% of US hospitals have a basic EHR system.
  3. 7.7% of UK hospitals use some form of EHRs with only 2.6% using it for electronic prescribing.
  4. Less than 0.5% of German hospitals use their EHR for electronic prescribing.
- Even when deployed in a hospital, they may be limited to certain wards. For example, UHG has 24 overnight wards (excluding theatres and surgical day ward), yet only 4 of these wards use an EHR system.
- EHR are large and expensive IT systems with long implementation and deployment cycles.
- Retrofitting of legacy EHR is too expensive.
- Hospital IT infrastructure cannot be changed too quickly.
  There is a discrepancy between the needs of clinicians on the ground and the pace at which IT improvements are implemented.

As a consequence the envisaged system operates in parallel to an installed EHR.
1.2. Research Objective

Manual drug-dosage calculation, particularly in secondary care, can be a difficult, cumbersome and potentially erroneous task, which should be automated as much as possible. In the absence of fully integrated and large scale EHR systems, suitable alternatives must be found. Therefore the objective of this research is to investigate a computer-supported drug dosage calculating system for hospital environments that fulfil all clinical requirements (as outlined in the previous section). Such a system allows clinical staff to access a drug-dosage calculation module from anywhere, while pharmacy administrators can design and validate the underlying drug dosage algorithms. In addition, pharmacy administrators can also sign off on individual dosage calculations. The focus of this research is on dosing medication in patients with kidney impairment (as further explained in chapter three).

1.3. Research Hypothesis

Primary Hypothesis: Web-based solutions provide a viable personalised (e.g. patient-centred) medication and dosage management system for hospitals. Such a system, even though separate and unconnected to any existing hospital-based EHR system, fulfils all major clinical requirements.

Secondary hypothesis: Such a system solves the perceived problems of:

1. Medication errors
2. Accountability and the cost of drugs
3. New, changing and complex dosage calculation regimes.

1.4. Research Methodology

The research involved identifying the problems associated with existing drug dosing approaches. The requirement specification was primarily developed through a collaborative partnership with the lead clinical pharmacist. Potential future stakeholder pharmacists were also consulted, in order to obtain feedback to further refine the model as required. Based on these requirements, a prototype was developed which was subsequently tested by clinicians in UHG. A questionnaire was
circulated to clinical pharmacists in UHG, in order to obtain a more formalised evaluation of the prototype. This facilitated further refinement of the system so as to make it more responsive to users’ needs.

1.5. Research Significance

This research outlines the importance of a drug dosing module in any hospital, irrespective of its technological maturity. It highlights the current problems faced by clinicians in hospitals for calculating the drug dosage levels, in particular, for low therapeutic index drugs. The significance of this research is that it shows how low-cost IT technologies can be used in hospitals to prevent medication errors, ensure patient safety, governance of prescribing across geographical distinct areas and more rapid and accurate feedback of prescribing patterns.

1.6. Thesis Overview

This thesis is divided into eight chapters.

Chapter one presents an overview of the thesis. It also explains the research area, objectives, hypothesis, methodologies and significance.

Chapter two focuses on electronic healthcare record systems used in hospitals. It differentiates between client-server, web-based and cloud based EHR systems and also provides a detailed review of their advantages and limitations.

Chapter three presents the overview of the drug dosing problems related to kidney impairment medication. It provides a brief introduction to human kidneys, performance metrics for kidney function, and the treatment of patients with kidney impairment and finally outlines problems with drug dosage calculations in such patients.
Chapter four introduces SQUID (System for Quality Use of Drugs), which addresses the problems outlined in the previous section. This chapter provides the high level architecture of the system.

Chapter five provides the implementation details of the SQUID application.

Chapter six focuses on the tools and technologies used while developing SQUID.

Chapter seven concerns the working model of the SQUID application, detailing the in-depth functionalities of each and every module. This chapter also presents the user feedback.

Chapter eight provides a conclusion of this research and discusses future work and recommendations.
2. Literature Review

2.1. Automation in Healthcare

In comparison to other industries, the healthcare industry, particularly secondary care, considerably lags behind with respect to automating manual processes (including dosage calculation). In order to speed up such processes, to attain a high quality of service and to reduce costs, an increased level of automation in hospitals is essential. This can be achieved by widespread deployment of information technology. For example, better decision support systems and the availability of patient information at the point of care, can reduce medication errors and increase patient safety.

To achieve automation in healthcare, the Institute of Medicine (IOM) promotes paperless records and electronic patient record systems in secondary care [11]. However, despite many initiatives and numerous advantages of such systems, their adoption is very low. Even in developed countries, the use of electronic record system is less than 10% [12]. Some of the reasons for this include [13]:

1. Lack of a standard framework
2. Lack of motivation
3. Lack of direct benefits for practitioners
4. Confusion about the concept

2.2. Healthcare Information Technology

Healthcare Information Technology (HIT) is the science which connects healthcare and information technology. It allows healthcare professionals to provide high quality care to patients. HIT systems can be used for: storing clinical data electronically, patient-level costing and insurance systems, educating patients through multimedia, exchanging healthcare information between various healthcare providers and in research and analysis of healthcare modules. Furthermore HIT
improves healthcare quality and productivity, prevents medical errors, reduces healthcare costs and decreases paperwork.

There is a range of different HIT system concepts deployed in secondary care and a variety of technical terms are in use. Some of these are mentioned below with a brief description:

1. **Computer-based Patient Record (CPR)**: This is an enterprise system with the capability of storing lifetime patient records. It contains information from all specialities and aims for interoperability, internationally.

2. **Electronic Patient Record (EPR)**: It is similar to CPR but does not contain lifetime patient records and stores only important information.

3. **Electronic Medical Record (EMR)**: Stores clinical information with full interoperability within hospitals.

4. **Digital Medical Record (DMR)**: It is a web-based patient record maintaining system.

5. **Patient Medical Record Information (PMRI)**: This is primarily used for health statistics.

6. **Personal Health Record (PHR)**: These types of system are managed and controlled by patients.

7. **Electronic Health Record (EHR)**: It is a generic term used for all electronic patient care systems.

Although there are many HIT concepts available, EHR is the most widely used. The remainder of this chapter focuses on the EHR system.

### 2.3. EHR Systems and their Functionality

An EHR system is defined as an electronic collection of health information concerning individual patients or an entire population. The collected information is maintained by healthcare providers. The information may include patient
demographics, medical history, immunisation status, laboratory test results, medication and allergies, radiology images and discharge information.

The eight core EHR functionalities as specified by IOM are [22]:

- *Health information and data*,
- *Result management*,
- *Order management*,
- *Decision support*,
- *Electronic communication and connectivity*,
- *Patient support*,
- *Administrative processes and reporting*,
- *Reporting and population health*.

### 2.4. Types of EHR Systems

Depending upon the architecture and connectivity type, EHR systems can be classified into three types:

1. **Client-Server based EHR**
2. **Web-based EHR**
3. **Cloud-based EHR**

A brief synopsis of these three types of EHR systems and their advantages and disadvantages is provided below.

#### 2.4.1. Client-Server Based EHR

A client-server EHR is based on client-server architecture, where the EHR software and data is shared between the server and clients. In this type of architecture, the server resides and is maintained on premise of the organisation. As the server resides in-house, the data communication is generally very fast when compared with other types of EHR. It is the responsibility of the IT administrator to maintain up-to-date versions (e.g. patch the system when needed) and to manage data back-ups. One
perceived problem here is the enormous increase in patient data in recent years [14] [15].

**Advantages**

- **Full control**: As the server is hosted locally within the hospital, the users have total control of the server and data.
- **Connectivity and speed**: As the server resides locally and the number of clients is limited to the hospital, the connectivity between the server and client is very fast.
- **Security**: Client-server EHRs are often isolated systems with limited internet connectivity. This reduces potential cyber-attacks from outside.

**Disadvantages**

- **Initial investment**: The initial investment is very high, when compared with other types of EHR. Along with the software, the user has to buy the hardware, server, workstation and databases.
- **Server maintenance**: The user will be responsible for maintaining the server. For this, the clinicians need to employ a professional IT person for monitoring and maintaining the server and other hardware.
- **Data protection**: The user is responsible for data protection against hardware or software failures. This requires the use of sophisticated data backup software.
- **Installation of upgrades**: All upgrades and software patches should be installed by the user themselves.
- **Multiple locations**: Dedicated WAN and LAN are required if the user wants to operate the software from multiple locations. Installation of network connections is expensive and hardware and software technical support is required.

Some of the existing client server based EHR systems [16] [17] [18] [19] [20] [21] are MediTech, Genesis Chiropractic solutions, AllScripts, NextGen, Cerner Ambulatory, IngenixCareTracker.
2.4.2. Web-Based EHR

In a web-based EHR system, the software system is deployed in a remotely hosted server. The users of this system have to access the information via the internet. This type of EHR allows the users to work from various locations and can retrieve medical data at any time. The advantages and disadvantages of this system are described below.

Advantages

- **Initial Investment**: It is not necessary to purchase any special hardware or software, only an internet connection is required to access the data.

- **Server maintenance**: is the responsibility of the vendor who provides the web server. So the user will not have to be concerned with maintaining the server.

- **Operational Cost**: The cost of using the web-based system can be paid monthly, which will be considerably less, compared to buying the whole system at once. The user only needs to pay for the modules which they use.

- **Access from anywhere, anytime**: As it is a pure web application, the user can access data from anywhere, at anytime and with any device which has the capability of connecting to the internet.

- **No installation or upgrades**: The installation or upgrades of the software will be completed at the server, so the user will be free of installation or upgrades at the system level.

Disadvantages/Limitations

- **Connectivity**: As this is a web application, to access data from the server, the client system should be connected to the server using the internet. If there is no internet connection, or if there is a connection failure, this system will not work.

- **Speed**: Access to the server data is dependent on the internet connection speed. The speed will be less than the client server model.

- **Security**: Data can potentially be accessed by unauthorised persons (e.g. hackers) as the data resides in a remote location.
Some of the existing client server based EHR systems [24] [25] [26] are MTBC, CX360 and TREAT.

2.4.3. Cloud Based EHR

“Cloud computing is Internet-based computing, whereby shared resources, software and information are provided to computers and other devices on demand.” [28]

Similar to grid computing, distributed computing and parallel computing, cloud computing is a combination of traditional computing technology, with network technology. It is built on powerful computing capability, through a large number of interconnected computing systems, using business models such as Software as a Service (SaaS), Platform as a Service (PaaS) and Infrastructure as a Service (IaaS) to provide powerful computing capacity to the end user. The services in cloud computing are dynamically scalable with virtualised resources. The main benefits of cloud computing includes [28]:

1. **Reduced cost model**: Using cloud, there is no direct investment in hardware or software resources. Most cloud systems work on a pay-per-use basis, the user only needs to pay for the services which they wish to use.
2. **Reliability**: The data in cloud can be stored in multiple redundant sites for securing business continuity and any disaster recovery.
3. **Scalability and Sustainability**: Scalability is the one of the core benefits of cloud computing. It allows user to have a flexible IT service that are scaled instantly to meet the operational needs and business processes. Cloud computing is an energy efficient IT system. With the modern large-scale data centres in place, it helps to reduce the business carbon footprint.

Cloud computing is still an evolving technology and despite the large number of benefits, there are also limitations [29]:

1. **Network Connection**: The upload and download speed of cloud computing is slower than a local server. If there is any network failure or a
1. Slow network connection at the user end of a cloud, then access to data will be either difficult or not possible.

2. **Data Security**: The clients do not have control over their own data in cloud. There might be chances of hacking or phishing attacks. Since the servers on cloud are interconnected, it is easy for malware to spread.

3. **Peripheral Connection**: Devices like scanners, printers might not work with the cloud due to the local installation of software. Integration of internal applications with those on cloud can be a complex process.

Some of the existing cloud-based EHR systems [30] [31] [32] are MedTouch, Mitichon and CareCloud. See also Figure 1 and 2.

![Figure 1. MediTouchiPad App](image)

CareCloud is a cloud-based EHR system. It provides practice management software and back office services to healthcare providers. CareCloud has more than 2,000
customers including hospitals and doctors with 4.5 million patient records. Figure 2 shows a patient record in a CareCloud system [31].

![CareCloud System](image)

**Figure 2. CareCloud System**

### 2.5. Conclusion

“The EHR provides the essential infrastructure required to enable the adoption and effective use of new healthcare modalities and information management tools such as integrated care, evidenced-based medicine, computer-based decision support, care planning and pathways and outcomes analysis” [35].

Although EHR systems have a great number of benefits, there are still barriers to overcome. As a result, the uptake of such systems is still very low. However, as seen in the previous chapter there is a need for IT-supported clinical solutions, for example in the area of dosage calculation. With the lack of integrated EHR systems
there is a need for alternative solutions. This research focuses on such alternative systems.
3. **Drug Dosing in Kidney Impairment**

3.1. **Introduction**

In the previous chapter, the advantages and disadvantages of EHR systems have been outlined. This chapter focuses on the drug dosing module, which could be a part of an EHR system taking kidney impairment as a use case. This chapter gives a brief introduction of the human kidneys and the stages of kidney failure. It also details the medications available to treat kidney failure, the key factors where clinicians may incorrectly treat patients with kidney failure and finally, the solutions available.

3.2. **Anatomy of Kidneys**

Kidneys are bean shaped organs located in the middle of the back, just below the rib cage on either side of the spine in the human body. The size of each kidney is about 11 to 14 cm in length, 6 cm in width and 4 cm thick, approximately the size of the fist. Figure 3 shows the size and location of human kidneys. The main function of the kidneys is to filter the blood in the body. While filtering the blood, it removes waste products and drugs from the body, maintains balance in bodily fluids, releases hormones for regulating blood pressures, produces important vitamins to keep bones strong and healthy and controls the production of red blood cells [36].
3.3. Estimated Glomerular Filtration Rate (eGFR)

In general, the two primary routes of drug elimination and metabolism are the liver and the kidneys. The kidneys have a critical role in cleansing the body of water soluble waste products. However, many medications are also eliminated via the kidneys. If a patient's kidneys are not fully functional, there is a risk of accumulation of drugs and consequent toxicity.

Kidney performance can be estimated via a clinical test called eGFR [38]. The eGFR tests the blood for creatinine. Creatinine is a by-product that comes from muscles. A clinician will use serum creatinine, age, sex, weight and height to calculate the GFR (in micromole per litre). There are several methods for estimating GFR. When determining doses for patients requiring drugs with a low therapeutic index, Cockcroft-Gault\(^1\) method is widely quoted and used by drug manufacturers. Irrespective of the exact method used, the calculation is complicated and time-consuming for individuals who are not experienced in such matters. This presents a major barrier to obtaining the correct dose every time, for each patient.

\(^1\)Cr\(\text{Cl} = (140\text{-age}) \times \text{Mass (in KG)} \times (0.85 \text{ if female})/72 \times \text{Serum Creatinine (in mg/dL)}\)
3.4. Kidney Failure

There are five stages of kidney failure, ranging from stage 1 to stage 5. Each stage is based on the function of kidneys, which is assessed using eGFR [37]. Stage 1 is considered as the early stage of kidney damage, it occurs when the eGFR value is greater than 90 ml/min. The second stage is when the eGFR value is between 60 and 89 ml/min. The third stage is when the eGFR value is between 30 to 59 ml/min. The fourth stage describes severe kidney damage with poor functioning, it occurs when the eGFR value is between 15 to 29 ml/min. The last stage is the end stage of kidney damage, with little or no kidney function and the eGFR value is less than or equal to 15 ml/min. Without intervention through dialysis it may lead to death.

3.5. Medication Prescription for Patients with Kidney Impairment

Drugs with a low therapeutic index (such as gentamicin) require individualised dosages for patients with kidney impairments. Pharmacologists must be very precise in determining the degree of kidney impairment, to ensure that the most appropriate dose is given to the patient. For gentamicin, for example, too much of a dose can result in kidney damage and too little of a dose will fail to treat the infection.

The main concerns while calculating drug dosage include [41]:

- Calculation complexity (see also Figure 4).
- Distractions from work such as bleeps, interruptions, sleep deprivation, multitasking and workload in general.
- Multi-step process for calculating a single dosage level; a series of steps has to be followed, such as calculating ibw (ideal body weight), adjusted body weight, CrCl and dosage regimen.
- Ignoring the assumptions that underlie calculations. For example, the importance of calculating ideal body weight from raw data, such as height or weight.
- Changing dosage requirements as a result of changes in a patient’s condition.
- Competency of healthcare staff in performing the calculations.
- Minor oversights such as decimal point error.
- Unit conversion confusion. For example, use of imperial measurement units in an equation designed for standard international expression of units, such as pounds for kilograms.

Considering these challenges, it was decided that an automation of the dosage calculation would result in more patients receiving the correct dose at the start.

![Flow Chart of a Drug Calculation for Gentamicin in Adults](image)

**3.6. Existing Medical Calculators**

Many existing online drug dosing calculators are available online. They can calculate creatinine clearance level, dosage levels for specific drugs and many other calculations. The major drawbacks for these systems are:

- They are not well documented
• Lack of confidence in using them
• Not validated in a transparent fashion
• Unreliable
• The formulas used are hidden in the backend
• The system may go down at any time
• They are not communicative
• No feedback mechanism

Medical Calculator is one example which is available at http://www.medical-calculator.nl/ website. Figure 5 shows the home page of this system, it can be used to calculate body mass index, GFR, body surface area, paediatric dosage level, mean arterial pressure etc. Even though these types of calculators are available, they might not be used in hospitals due to the previously mentioned challenges.
Figure 5. Medical Calculator
Another example is shown in Figure 6, which is a creatinine clearance calculator taken from the MDCalc website².

![Figure 6. Example of Medical Calculator](image_url)

### 3.7. Conclusion

This chapter provides an overview of human kidneys, the stages of kidney failure, levels of eGFR and medication for treating kidney failure. It also describes the importance of calculating drug dosage levels, available online solutions and their limitations. The next chapter discuss SQUID which is a use case for solving these problems.

4. SQUD

4.1. Introduction

SQUD (System Quality Use of Drugs) is a drug management framework, which addresses a number of problems and limitations in clinical drug management as outlined in previous chapters. From a high-level perspective, the advantages of this system are:

- Accessible from the patient’s bedside to facilitate decision support systems irrespective of location.
- 100% accurate, free from erroneous calculations.
- Robustly validated, the validation process is transparent so that clinicians have confidence in the robustness of the system.
- Capable of sending instant message to pharmacy staff.
- Extensible to many drugs through the development of a solid platform for generic use.
- It is reliable as the drug dosing regimens are entered into the application and thoroughly validated by the pharmacy administrator in the hospital itself.

4.2. Design of SQUD

This section describes the aspects of SQUD system design. Figure 7 shows the basic modules of the SQUD application.

The design of this system can be split into two parts:

1. Design of a drug dosage calculator frontend for clinicians.
2. Design of a framework for the pharmacy administrator to generate drug dosage calculations.
The above design can be achieved by building a web-based application, which serves as a framework for pharmacy administrators. It is used to generate drug dosing protocols, which are then used by clinicians.

4.3. SQUD Flow Diagram

The following steps describe the envisaged deployment of this system, while its flow diagram is also shown in Figure 8:

1. The pharmacy administrator logs into the application anywhere via the Internet and can create, validate, update and delete the drug protocols.
The created drug protocol is saved in the web server.

Clinicians have to register with the system prior to using it. After registering they can use the calculator via web browser and smartphones.

Smartphones and PDAs which are enabled with Wi-Fi or 3G can login to the application via the Internet.

4.4. Conclusion

This chapter describes the design and high level flow of the SQUID web application. The next chapter provides the implementation details of this web application.
5. SQUID IMPLEMENTATION

5.1. Introduction

The generic dosage calculator is implemented using Java technologies. Java Enterprise Edition (JEE) is used to build the web architecture. The web architecture is divided into two sections; the administrator and the clinician section.

5.2. Administrator Section

Administrator section represents plug-in type architecture for creating new drug dosage protocols, for any drugs affected by kidney impairment. There are four options available to the administrator, they are:

1. Create new protocol
2. Validate protocol
3. Update protocol
4. Delete protocol

Figure 9 shows the administrator options page.

![Figure 9. Administrator Page](image-url)
By selecting the ‘Create new protocol’, the administrator creates the drug dosing protocols based on creatinine clearance, dosing type and dosing weight. These fields are required for calculating the drug dosage level. There is also an option for entering dialysis information for those patients who already rely on dialysis. This is shown in Figure 10 and 11. After entering all the information, the administrator can test the protocol. If the desired output is shown, the administrator can now save this protocol. Example of the test protocol phase is shown in Figure 12.
<table>
<thead>
<tr>
<th>Enter Maximum dose</th>
<th>2000.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enter Rounding dose</td>
<td>500.0</td>
</tr>
<tr>
<td>Enter URL for reference</td>
<td>index.php?q=node/251</td>
</tr>
<tr>
<td>Enter Haemodialysis Loading Information</td>
<td>2000mg every 8 hours only if life-threatening and/or on advice of microbiology, otherwise use maximum dose of 1000mg every 8 hours.</td>
</tr>
<tr>
<td>Enter CAHDF Loading information</td>
<td>Check with Microbiology and Renal teams.</td>
</tr>
<tr>
<td>Select Population type</td>
<td>Adult</td>
</tr>
<tr>
<td>Additional information</td>
<td>MicroID and consider REGULAR dosage review if symptoms improve with aim of reducing dose to 1g every 6 hours to minimise chances of accumulation (and hepatotoxicity).</td>
</tr>
</tbody>
</table>
When the administrator saves the protocol, it is saved in the webserver as two XML files. One XML file appends the new drug name and its properties (e.g. validated, archived and deleted), while the other XML file is created with the drug name itself and has all the information that has been entered by the administrator during the creation of the protocol. Figure 13 and 14 shows the above described XML files respectively.
The new drug protocol will be sent to the validation process. Until the protocol is validated, this drug will not be ready for use. The administrator can validate the drug using the validation option. In this stage, the administrator selects the drug and the number of test cases and an excel file with test data will be generated, according to the number of specified rows. The test data consists of random values, which contain data such as age, weight, height, serum, ibw, gender, obesity percentage and finally the dosage level. These values will be verified manually by the clinical pharmacists. If the manual calculation matches the generated values then the administrator can sign the file and upload it to the server. The uploaded drug file is marked as validated and is ready to use. The validation page, selection of drug and rows, generated values and manually verified values are shown in Figures 15, 16, 17 and 18 respectively.
The validation process provides a robust core for the application. The administrator also has the option of updating or deleting an existing drug.
<table>
<thead>
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<th>Weight</th>
<th>Height</th>
<th>Serum</th>
<th>Gender</th>
<th>IBW</th>
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</tbody>
</table>

Figure 17. Downloaded Validation File
In the clinician section, the clinicians can calculate the drug dosage level and also view patient records. Figure 19 shows the clinician options page. The clinician web application parses one of the XML file for all the drug names which have been successfully validated. All validated drugs are displayed in a list, from which the clinician can choose one. Figure 20 shows an example of the selection of a drug from the list.
The system then opens the XML file associated with the drug name and parses the file for retrieving the dosing regimen specification, dosing type and dosing weight. This data is used while calculating the dosage level. The clinicians have to enter the patient details such as ID, age, weight, height, serum creatinine and gender, and click the calculate button. An example of the gentamicin drug calculation is shown below in Figure 21. After calculating, the drug dose is displayed (Figure 22). The clinician can request a copy of drug and calculations, by specifying the clinical department by clicking the send drug option. The system then sends an email to the pharmacy staff specifying the drug name, dosage level and area of use. The values are also updated in the database for future verification and auditing purposes.
Figure 21. Input Patient Details

Figure 22. Calculated Output Values
5.4. **Smart Phones and Tablet PCs’**

Smart phones and tablets which are enabled with Wi-Fi or 3G connectivity, can access this application using the www.squd.eu URL. Figure 23 shows the SQUD application being used in an iPhone safari browser.

![Figure 23. SQUD Application Accessing in iPhone](image-url)
5.5. Security-Authorisation and Authentication

As this application deals with very sensitive healthcare data like patient and clinician details, the data in the server should be secure and it should be accessible only by authorised individuals.

To use this application, any clinician has to register with the system. The registration process is shown in the Figure 24. The clinicians have to enter: their name, email id (this will be their login id for future use), create a password, the name of the hospital where they work, their contact number, bleep number, speciality and a small arithmetic value to prevent spam registrations by a remote computer. MD5 encryption is used to store the password in the database for additional security.
After the clinician successfully enters all the values and clicks on registration, an email will be sent to the administrator with the values specified in the registration form. The administrator checks the details and if the details are genuine, they can activate the user by clicking the activation link which is provided in the email.

Once the user is successfully activated, they can login into the SQUD web application using their login credentials.

5.6. Deployment

Once the web application has been developed and thoroughly tested on the local machine, it must be deployed to an external web server in order to be available to all users.
There were two different servers used initially:

**Amazon Elastic Compute Cloud (Amazon EC2)**

Initially the application was deployed in an Amazon EC2 server. The main reasons for choosing this related to its cloud capabilities i.e. its virtual computing environment, load balancing and that it’s cost effective. Even though there are many advantages, the limitation of using this server was the confidentiality of patient data.

**Hosting Ireland Server**

Once the application was tested successfully in the local server, it was then deployed on a private server with anonymised patient fields. The domain chosen is squd.eu and hosting services are provided by the Hosting Ireland Company (http://www.hostingireland.ie). Hosting Ireland is a service provider which provides domain name registration and hosting services including online back-up of servers, email hosting, email back-up, anti-virus protection, spam filtering, e-commerce solutions etc. The servers of Hosting Ireland are located in Dublin.

### 5.7. Conclusion

This chapter focused on the implementation of the SQUD web application. It discussed detailed information on the administrator and clinician implementation. It also highlights security and authentication implementation and deployment of the web application in the server. The next chapter outlines the tools and technologies used while implementing the SQUD web application.
6. TOOLS AND TECHNOLOGIES

6.1. Introduction

This chapter describes in-depth details of the tools and technologies used in the implementation of this research. The SQUD web application is developed using Java programming language, facilitated by Apache Struts and the Hibernate frameworks. MySQL is the database chosen for storing the clinical data, while Apache Tomcat is chosen for the web server. In addition to these technologies, XML, wireless communication technologies and software testing are also explained.

6.2. JAVA

The SQUD web application is developed using Java programming language. Java is a programming language based on object-oriented principles. Java was initially developed by Sun Microsystems, which is now part of the Oracle Software foundation. The key features of Java are platform independency, security, multi-threading, robustness and dynamism. Applications developed in Java can run on any operating system that supports the Java VM. A wide range of applications have been developed using the Java language, ranging from small desktop applications such as games, to large enterprise application like telecommunication systems. As there is a lot of versatility in developing such applications, the Java community has divided the Java platforms into three types [42]:

1. Java Platform Standard Edition (Java SE)
2. Java Platform Enterprise Edition (Java EE)
3. Java Platform Micro Edition (Java ME)

**Java SE**: It contains a set of API’s for developing and deploying Java applications, on desktops, servers and also on embedded devices. Java SE core packages support features such as user interface design, I/O, mathematical operations, database connectivity and security [43].

**Java EE**: Java EE is built on top of the Java SE platform and contains additional API’s and runtime environments for developing large-scale, multi-tiered, reliable,
scalable and secured enterprise (web) applications. Java technologies like Servlets, JSP, JSF, EJB, JDBC, JPA, and JTA are part of Java EE [44].

**Java ME**: Java ME platform contains the Java SE API’s and additional API’s for developing applications for embedded devices and mobile platforms [45].

Figure 25 shows the three different Java platforms.

![The JAVA 2 Platform Edition](image)

**Figure 25. Java 2 Platform Editions**

### 6.3. SQUD Web Application Development

Java EE technologies such as Servlets and Java Server Pages (JSP) are used for developing the SQUD web applications. The developed application is deployed in apache tomcat web server. The web server runs the application and makes it available to the users through the HTTP protocol. In order to make the application development faster and easier, Apache Struts framework has been used. The details of the apache struts framework such as its underlying design pattern, architecture are discussed in the next section.
6.3.1 Apache Struts Framework

Apache Struts is an open source framework from the Apache Software Foundation for developing web based applications, using standard Java EE technologies, for example, JSPs, Servlets and JavaBeans. It is easy to create maintainable, extensible and flexible web applications utilising Struts. Struts use the Model 2 MVC (Model View Controller) design pattern [46].

MVC Design Pattern

MVC design pattern, the model contains the business logic of the application and the data sources. View is the user interface that displays the model information. Controller controls the flow of the application, according to the user interaction. Based on the controller architecture, MVC Design Pattern is classified into two types; Model 1 and Model 2 architectures.

Model 1 Architecture:

Model 1 architecture is used for developing small scale web applications. In this model, the component which accepts the user requests is also the component for sending the response, usually which are JSPs. The architecture of model 1 is shown in Figure 26.

Figure 26. MVC Model 1 Architecture
1. The browser sends a request to the JSP page.
2. The JSP page communicates with the JavaBeans.
3. The JavaBeans send the user request to the business logic.
4. The Business logic executes the users request; if necessary it interacts with the databases and updates the JavaBeans.
5. The JSP page retrieves information from JavaBeans and sends the response to the browser.

Model 2 Architecture

Model 2 Architecture is used for developing large-scale web applications. Model 2 architecture separates the request handling logic, from the presentation logic. The incoming request from the browser will be handled by the Controller Servlets. JavaBeans are the intermediate component which stores the processed data and delivers it to the view as required. The JSPs extract the information from the JavaBeans and send the response to the client. The architecture of Model 2 is shown in Figure 27.

Figure 27. MVC Model 2 Architecture

1. The browser sends the request to the controller servlet.
2. The controller servlet instantiates the JavaBean components and executes the business logic of the user request.
3. The controller requests the specified view (JSPs).
4. The JSP page loads the information from the JavaBean.
5. The JSP page sends the response to the browser.

**Struts Architecture**

Struts architecture is based on Model 2 MVC design pattern, it consists of five key parts:

1. Action Servlet
2. Action Classes
3. Java Server Pages
4. Action Forms
5. Struts Configuration Files.

1. **Action Servlet**: The Struts framework provides the controller servlet (Action servlet) for the web application. Action servlets are automatically registered in the deployment descriptor file (web.xml). The Action servlet uses the Struts configuration file (struts-config.xml) to map the incoming request to the Action objects, and instantiates the associated Action Forms to store the form data. The flow of the Struts framework is shown below in Figure 28.
Deployment Descriptor: The web.xml file in the Struts application is known as the deployment descriptor file. The role of the web.xml file is to configure the action servlet, the Struts configuration file and provides a definition for the URL pattern. The web.xml file below is the deployment descriptor file for the SQUD web application.

```xml
<?xml version="1.0" encoding="UTF-8"?>
version="2.4"
  <servlet>
    <servlet-name>action</servlet-name>
    <servlet-class>org.apache.struts.action.ActionServlet</servlet-class>
    <init-param>
      <param-name>config</param-name>
      <param-value>/WEB-INF/struts-config.xml</param-value>
    </init-param>
    <load-on-startup>2</load-on-startup>
  </servlet>
  <servlet-mapping>
    <servlet-name>action</servlet-name>
    <url-pattern>*.do</url-pattern>
  </servlet-mapping>
  <welcome-file-list>
    <welcome-file>index.jsp</welcome-file>
    <welcome-file-list>
  </welcome-file-list>
</web-app>
```

Code 1 web.xml the Deployment Descriptor File
2. **Action Classes**: Struts framework is a set of jar files (Java archive) and each jar file contains packages. The Action classes are present in "org.apache.struts.action.Action" package. The Action classes have one method called ‘execute()’. The action object processes the data stored in the ActionForm bean, by using the execute method. It invokes the application business logic. Action object acts as a wrapper to the business logic and provides an interface to the applications model layer. Once the action object processes the data in ActionForm bean, it forwards the result to the appropriate view.

   The action classes in SQUID include:
   - AdminLoginAction
   - ClinicianLoginAction
   - ClinicianDrugCalculatorAction
   - DrugCalculatorAction
   - LogoutAction
   - PatientRecordAction
   - RegistrationAction
   - UpdateAction
   - ValidateAction

3. **ActionForm**: ActionForms are standard JavaBean components. They consist of properties which are used in views, along with public getters and setters methods. ActionForms are used to store data between requests. It resides in the "org.apache.struts.action.ActionForm" package. In Struts, for every HTTP request there must be an ActionForm.

   ActionForm Classes of SQUID: All the action forms are placed in com.squd.struts.form package, the action forms used in this application are:

   - AdminLoginForm
   - ClinicianLoginForm
   - ClinicianDrugCalculatorForm
   - DrugCalculatorForm
- PatientRecordForm
- RegistrationForm
- UpdateForm
- ValidateForm

Below is an example of ActionForm (AdminLoginForm) code.

```java
package com.squd.struts.form;
import java.util.ArrayList;

public class AdminLoginForm extends org.apache.struts.action.ActionForm {
    private static final long serialVersionUID = -7015231902054223047L;
    private String userName;
    private String password;
    private String name;
    private String err;
    private ArrayList<String> drugList = new ArrayList<String>();

    public String getUserName() {
        return userName;
    }

    public void setUserName(String userName) {
        this.userName = userName;
    }

    public String getPassword() {
        return password;
    }

    public void setPassword(String password) {
        this.password = password;
    }

    public String getName() {
        return name;
    }

    public void setName(String name) {
        this.name = name;
    }

    public String getErr() {
        return err;
    }

    public void setErr(String err) {
        this.err = err;
    }

    public String[] getDrugList() {
        return drugList.toArray(new String[drugList.size()]);
    }

    public void setDrugList(String[] drugList) {
        this.drugList = new ArrayList<String>(Arrays.asList(drugList));
    }
}
```

Code 2 AdminLoginForm - An Example of ActionForm

4. Java Server Pages (JSP): JSPs are used for displaying the response to the end user i.e. browser. The Struts framework provides custom tag libraries such as HTML tags, Bean tags and Logic tags. Using these tag libraries makes the development of web pages faster and easier. Some of the JSP pages in SQUD include:

- Index.jsp
• AdminLogin.jsp
• ClinicianLogin.jsp
• DrugCalculator.jsp

Example JSP code of DrugCalculator is shown below:

```xml
<%@taglib uri="/WEB-INF/struts-logic.tld" prefix="logic" %>
<%@taglib uri="/WEB-INF/struts-bean.tld" prefix="bean" %>
<%@taglib uri="/WEB-INF/struts-html.tld" prefix="html" %>

<!DOCTYPE HTML PUBLIC "-//W3C//DTD XHTML 1.0 Strict//EN"
"http://www.w3.org/TR/xhtml1/DTD/xhtml1-strict.dtd">
<html class="win chrome chrome7 webkit webkit5 firefox firefox3 gecko gecko1"
xmlns="http://www.w3.org/1999/xhtml" xml:lang="en" lang="en">%>  
<head>
</head>
<title>SQUD Drug Calculator</title>
<%@ include file="js/DrugCalculator.js" %>
<%@ include file="tags.jsp" %>
<%@ include file="header.jsp" %>
<%@ include file="template/body/drugCalculator.jsp" %>
<%@ include file="footer.jsp" %>
</html>
```

5. Struts Configuration File: The struts-config.xml is known as Struts configuration file. There is only one struts-config.xml file for the entire
application. Action servlet uses this configuration file to understand the relationship between the View and Controller components of the Struts application. As soon as the application is deployed, an action servlet loads this file and keeps the application.

6.4. MySQL

MySQL is an open source relational database management system [47]. This database stores all the clinical data for the SQUUD web application. There are four tables in this database:

1. **Admin**: contains the administrator login details such as username and password.
2. **Clinicians**: contains the details of the clinicians who have been registered with the SQUUD application. The table consists of 9 columns, such as name, email, password, hospital name, speciality, contact number, bleep number, uid and active status.
3. **Patient Details**: contains the drug dosing information for a particular patient such as patient id, name of the drug given, time and date, dosage level, age, weight, height, serum level and creatinine clearance level.
4. **Drug List**: contains the details of the drugs which are used while calculating the dosage levels. The table contains the information about the drug such as whether the drug has been validated, tested, deleted, or archived and validation file details.

Figure 28 shows the tables of SQUUD database, it contains the field names and their attributes.
The view of the MySQL drug list table with the data is shown in Figure 28.
6.5. Hibernate

Hibernate is the ORM (Object Relational Mapping) tool used in the SQUD application, it maps Java objects to relational database tables and vice-versa. Hibernate is developed on top of Java DataBase Connectivity (JDBC). Hibernate provides high-performance object relational persistence and query service for Java. Hibernate lets developers develop persistent classes following common Java idioms including association, polymorphism, inheritance and composition, and Java collection framework [48].

Hibernate Query Language is an object oriented extension to the SQL. It provides a bridge between the object and relational worlds. It also provides the data query and retrieval facilities that considerably decrease the development time. It is also used in stored procedures to implement business logic in databases.
### 6.5.1 Hibernate Configuration File

The Hibernate configuration file is an XML file. It contains the mapping information that defines how Java classes relate to database tables. Mapping information such as the database name, driver class details, database connection URL, username and password details and related hibernate mapping details are placed in the XML tags of this configuration file. This configuration file is named as hibernate.cfg.xml, below is the hibernate.cfg.xml file used for the SQUD web application.

```xml
<hibernate-configuration>
    <session-factory>
        <property name="hibernate.dialect">org.hibernate.dialect.MySQLDialect</property>
        <property name="hibernate.connection.driver_class">com.mysql.jdbc.Driver</property>
        <property name="hibernate.connection.url">jdbc:mysql://localhost:3306/s555456_hmc</property>
        <property name="hibernate.connection.username">root</property>
        <property name="hibernate.connection.password">xyz123</property>
        <property name="connection.pool_size">1</property>
        <mapping resource="com/squd/hibernate/config/Admin.hbm.xml" />
        <mapping resource="com/squd/hibernate/config/PatientDetails.hbm.xml" />
        <mapping resource="com/squd/hibernate/config/drugList.hbm.xml" />
        <mapping resource="com/squd/hibernate/config/clinician.hbm.xml" />
    </session-factory>
</hibernate-configuration>
```

Code 4 Hibernate Configuration file

### 6.5.2 Hibernate Mapping Files

The object relational mappings are defined in a XML file, namely a Hibernate Mapping file. This mapping file contains the database table and the instructions to map the defined Hibernate persistent class. An example of a Hibernate Mapping file is shown below. This file maps the drug list table to the DrugList POJO class.
6.5.3 Hibernate Persistent Classes

Hibernate persistent classes are Java classes. The instances of this class are stored in the databases. These persistent classes follow POJO (Plain Old Java Object) programming model. These classes should contain only a default constructor. They should contain a unique id, for identification of objects, between Hibernate and the database. All the attributes that are part of persistent should be declared as private and have getters and setters methods.

The persistent class for DrugList mapping file is shown below:

```java
package com.squd.hibernate.dao;

public class DrugList implements java.io.Serializable {
    private static final long serialVersionUID = -5499786538579771589L;
    private String drugName;
    private boolean validated, tested, deleted, archived;
    private int sno;
    private byte[] uploadFile;
    private String validatedFile;

    public String getDrugName() {
        return drugName;
    }
}
```
public void setDrugName(String drugName) {
    this.drugName = drugName;
}

public boolean isValidated() {
    return validated;
}

public void setValidated(boolean validated) {
    this.validated = validated;
}

public boolean isTested() {
    return tested;
}

public void setTested(boolean tested) {
    this.tested = tested;
}

6.6. XML

XML (Extensible Markup Language) is a technology that is used to create new markup languages. Creating a new markup language means that the user can define their own structural rules for storing the data in a document. XML documents can be created and consumed in any language. They can be transported over a variety of protocols, independent of the operating system. The structure rules for a XML document are specified using the two popular technologies; Document Type Definition (DTD) and W3C XML Schema.

In SQUD, the entire drug dosing data is stored in XML files. These XML files are generated by the web based application using Java technology. There are several methods in Java for creating and accessing the XML data. These methods are present in jar files JAXP (Java API for XML Processing) and JAXB (Java API for XML Binding).

In JAXP there are two types of APIs; DOM (Document Object Model) and SAX (Simple API for XML parsing). In the SQUD web application the parsing is done using a DOM parser. DOM accesses the XML document as an object tree, it traverses
through the all elements of the tree and has the ability to read and write the XML files.

Below is the Java code for parsing the drug files [51]:

```java
import org.w3c.dom.*;
import javax.xml.parsers.*;
import javax.xml.transform.*;
import javax.xml.transform.stream.*;
import java.util.ArrayList;
public class DrugListXMLParser {
    public DrugListXMLParser() {
    }
    public String validate(String drugName, String dosageWeight, float[] min, float[] max, float[] amt, int[] freq, String dosingType, String url, String haemodialysis, String cavhdf, String populationType, float maximumDose, float roundingDose, String addInfo) throws javax.xml.parsers.ParserConfigurationException, javax.xml.transform.TransformerException, javax.xml.transform.TransformerConfigurationException {
        DocumentBuilderFactory factory = DocumentBuilderFactory.newInstance();
        DocumentBuilder builder = factory.newDocumentBuilder();
        DOMImplementation impl = builder.getDOMImplementation();
        Document doc = impl.createDocument(null, null, null);
        Element e1 = doc.createElement("drug-calculator");
        doc.appendChild(e1);
        Element dose = doc.createElement("drug");
        dose.setAttribute("dosingweight", dosageWeight);
        e1.appendChild(dose);
        dose.setAttribute("name", drugName);
        e1.appendChild(dose);
        dose.setAttribute("dosingType", dosingType);
        e1.appendChild(dose);
        dose.setAttribute("url", url);
        e1.appendChild(dose);
        dose.setAttribute("populationType", populationType);
        e1.appendChild(dose);
        dose.setAttribute("maximumDose", Float.toString(maximumDose));
        e1.appendChild(dose);
        dose.setAttribute("roundingDose", Float.toString(roundingDose));
        e1.appendChild(dose);
        for (int i = 0; i < 5; i++) {
            int j = i + 1;
            String r = "range" + Integer.toString(j);
            Element range = doc.createElement(r);
            String minValue = Float.toString(min[i]);
            String maxValue = Float.toString(max[i]);
            String amtValue = Float.toString(amt[i]);
            String frequency = Integer.toString(freq[i]);
            range.setAttribute("min", minValue);
            e1.appendChild(range);
        }
    }
```
range.setAttribute("amt", amtValue);
e1.appendChild(range);
range.setAttribute("max", maxValue);
e1.appendChild(range);
range.setAttribute("freq", frequency);
e1.appendChild(range);
}
Element dialysis = doc.createElement("dialysis");
dialysis.setAttribute("haemodialysis", haemodialysis);
e1.appendChild(dialysis);
dialysis.setAttribute("cavhdf", cavhdf);
e1.appendChild(dialysis);
dialysis.setAttribute("addInfo", addInfo);
e1.appendChild(dialysis);
// transform the Document into a String
DOMSource domSource = new DOMSource(doc);
TransformerFactory tf = TransformerFactory.newInstance();
Transformer transformer = tf.newTransformer();
transformer.setOutputProperty(OutputKeys.METHOD, "xml");
transformer.setOutputProperty(OutputKeys.ENCODING, "ISO-8859-1");
transformer.setOutputProperty("{http://xml.apache.org/xslt}indent-amount", "4");
transformer.setOutputProperty(OutputKeys.INDENT, "yes");
java.io.StringWriter sw = new java.io.StringWriter();
StreamResult sr = new StreamResult(sw);
transformer.transform(domSource, sr);
String xml = sw.toString();
return xml;
}

6.7. Wireless Communication Technologies

The SQUID web application can be accessed on mobile phones and on tablets PC’s with wireless communication technologies. This section gives brief information of wireless technologies such as mobile communication and Wi-Fi.

6.7.1 Mobile Communication

Based on the data, speed and technology used in mobile communication, at present there are 4 generations. Table 1 compares the generations of mobile communication technologies.
<table>
<thead>
<tr>
<th>Generation</th>
<th>Technology</th>
<th>Maximum download Speed</th>
<th>Application</th>
<th>Decade</th>
</tr>
</thead>
<tbody>
<tr>
<td>1G</td>
<td>FDMA</td>
<td>NA</td>
<td>Voice (analog traffic)</td>
<td>1980’s</td>
</tr>
<tr>
<td>2G</td>
<td>TDMA(GSM) and CDMA</td>
<td>9.6 KBPS</td>
<td>Voice, SMS, CS (circuit switch) data transfer</td>
<td>1990’s</td>
</tr>
<tr>
<td>2.5G</td>
<td>TDMA(GPRS)</td>
<td>35 to 171 KBPS</td>
<td>WAP, MMS, basic internet access (E-mail)</td>
<td>2000’s</td>
</tr>
<tr>
<td>2.75G</td>
<td>TDMA(GPRS+EDGE)</td>
<td>120 to 384 KBPS</td>
<td>WAP, MMS, high speed internet access (AV)</td>
<td>2000’s</td>
</tr>
<tr>
<td>3G</td>
<td>WCDMA(UMTS+HSPA)</td>
<td>600KBPS to 10 MBPS</td>
<td>Video conference, video on demand, Mobile TV, Telemedicine, GPS</td>
<td>2000’s</td>
</tr>
<tr>
<td>3.9G</td>
<td>FDMA(LTE)</td>
<td>Upto100 MBPS</td>
<td>Same as 3G with greater speed</td>
<td>2010’s</td>
</tr>
<tr>
<td>4G</td>
<td>IMT</td>
<td>Upto1 GBPS</td>
<td>With much higher speed</td>
<td>2010’s</td>
</tr>
</tbody>
</table>

Table 1. Mobile Technology Generations

At present the phones and tablet PC’s which are enabled with 2G or 3G and Wi-Fi connection can access the SQUD web application. The details of Wi-Fi are discussed in the next section.

6.7.2 Wi-Fi

Wi-Fi is a technology for connecting two electronic devices for the exchange of data, mainly internet using radio waves. Any Wireless Local Area Network (WLAN) devices that are based on IEEE 802.11 standard are called Wi-Fi. Wi-Fi works on 2.4 GHz and 5 GHz frequencies. Devices such as smartphones, tablet PC’s, game consoles and laptops are enabled with Wi-Fi technology. These devices connect to a network resource such as the internet, via wireless network access points called hotspots. Hotspots can be implemented anywhere such as in hospitals, airports, coffee shops, trains, buses. Mobile phones that do not have a data package (2G or 3G) can connect to the hotspot and use internet access, thus facilitating access to the SQUD web application.
6.8. Apache Tomcat Server

Tomcat is an open-source web server, developed by the Apache software foundation. The web applications written in Java technology can be deployed in a Tomcat server. Files which are used while developing the SQUD web application, such as all the Java classes, JSP pages, HTMLs, XMLs and libraries are grouped together in a war file (web archive) and deployed in a Tomcat server. The deployed web application can be accessed via HTTP protocol, using URL, from any web browser.

6.9. Software Testing

Testing is an important process in the software development life cycle. There are many types of testing in software. Some of them are listed below [49]:

- Functional Testing
- Non-Functional Testing
- Sanity Testing
- Smoking testing
- AdHoc Testing
- Retesting
- Regression Testing
- Performance Testing

For the SQUD applications functional testing has been conducted. Functional testing is a type of black box testing in which test cases are written and executed based on the software specification documentation.

Figure 26 shows a test case written for the administrator section of the application. It contains the details of the step number (which is a unique), step name, step description, the expected result, actual result and the final output (pass or fail). The appendix page contains all the test cases.
### 6.10. Conclusion

The tools and technologies such as Struts framework, Hibernate framework, MySQL, XML, wireless communication technologies and software testing which assisted in developing this research module have been discussed in this chapter. The next chapter provides an overview of the working model of the SQUID web application.
7. **Working System**

This chapter describes the working model of the SQUD web application and summarises end-user feedback.

7.1. **Current Status**

At this stage, the application has been developed and tested thoroughly. It is deployed in a private server which is based in Dublin, Ireland. The application can be accessed using the URL www.squd.eu. Currently there is an administrator for this application, who is able to create, validate, update and delete drug protocols. To date (August 2013), 25 drugs have been created and successfully uploaded in the server. Out of these 25, 11 drugs have been validated and are ready for use in hospitals, while 15 Clinicians have been registered with the system. The developed calculator is being used at patient’s bedsides via Internet-enabled smart phones. The built-in validation process works well for any empiric regimen, to ensure that protocol is 100% accurate. This system is capable of sending instant notification to the pharmacists via email. Information about dialysis such as intermittent haemodialysis and continuous arteriovenous haemodialysis can also be stored. Figure 32 shows the comparison of speed of gentamicin dosing when comparing manual versus desktop PC application. The result of gentamicin calculator, mean calculation time with calculator is 21 seconds as compared to over 200 seconds.
7.2. The Questionnaire

In order to obtain user feedback on the developed system, a survey was conducted and circulated around NUIG Medical School, HPAI (Hospital Pharmacists Association of Ireland), EAHP (European Association of Hospital Pharmacists) and in social media including Facebook and LinkedIn. The survey and the user feedbacks are discussed below:

**QUESTION 1**

**Choose the most suitable answer:**

- I review/prescribe medicines which are nephrotoxic
- OR which require dosage reductions due to renal impairment
QUESTION 2

In relation to eGFR.....

- I do NOT use eGFR to prescribe doses of toxic drugs or in patients with extremes of body weight.
- I DO use eGFR to prescribe doses of toxic drugs or in patients with extremes of body weight.
QUESTION 3
When estimating GFR using Cockroft and Gault, I use an electronic calculator

- Yes
- No
- N/A
QUESTION 4

If you do use an electronic calculator, list the app/product that you use.

Received 7 responses

- Carboplatin
- iphone 4S
- GUH Antimicrobial App
- GAPP, Sanford guide app, MedCalc Pro, Scottish Consortium
- GAPP- UCH Galway designed app
- Samsung Galaxy S3 Calculator
- Developed myself on Pendragon Forms using the equation
QUESTION 5
Please log-in to http://www.squad.eu by selecting "Clinician" on the menu, using the following credentials: Email address: "rxuchg@gmail.com" Password: "valid47days" Choose the NO DIALYSIS option. Calculate a gentamicin, enoxaparin, rivaroxaban and vancomycin dose, then choose the most suitable answers below.

CAUTION: Read the statements carefully to ensure your answers are accurate.

- I would be VERY INTERESTED in using this product
- I found the product VERY difficult to use
- I would like to use this all the time for calculating renal doses
- I would NOT recommend this product to other people
QUESTION 6

What aspects of this calculator frustrate or annoy you?

Received 11 responses

1. CHOICE OF 'NO DIALYSIS 'NEEDS TO BE SPECIFIED
2. The formula behind the interface must appear to the doctor who use it, and the possibility to register each calculate operations
3. No option for peritoneal dialysis
4. I've found it easy to use
5. The fact that you needed to know the patient's weight and height in kg and cm with no option for inches or lbs
6. Lots of the URL reference links don't work for the drugs above esp those on CAVHDF or dialysis. I thought it was unusual to chose the default dose of meropenem as 2g tds iv (from experience the majority of infections are treated with a dose of 1g tds) A more direct comment about Riveroxaban and choice in renal impairment, its good that it says choose warfarin - are all NOACs to be included? Enoxaparin wasn’t working
7. Not much help for dialysis patients as the answer is usually "see renal drug handbook". One dose came back as 0mg. I think it should make a clear statement "not recommended for this level of renal function". There is a lot of information visible on the screen (3 different body weights). It is not necessary to know these if the drug dosage calculation has been done for you. Should these be hidden and you can click to see them if required?
8. height restrictions - can't be used for paediatric patients
9. When calculating the gentamicin dose the calculator gives you actual wgt, ideal wgt and adjusted body wgt but does not tell you what wgt was used to calculate the dose or what the mg/kg dose is. i.e. 3mg/kg, 4mg/kg etc since some hospitals dose gent on ideal wgt and some on actual up to a certain wgt this should be clearer. In our hospital we would dose gent for this lady (61 yrs, 168cm, 78kg, cr 80 giving ideal wgt of 59.9kg and crcl of >60ml/min) at 5mg/kg based on ideal body wgt which gives a dose of approx 300mg but your calculator suggests 260mg which I assume is 4mg/kg. no problems with enoxaparin. the calculated creatinine clearance
should be specified as MDRD or C &G. I assume C&G but this should be specified. vancomycin: I think it should be made clearer that you are calculating ideal body just to calculate crcl and that the actual dose to give is correctly based on acutal wgt even if the patient is overwgt. i know the calculator will do that for you but i think that it should clear so that the doctors can understand what they are prescribing. also the vanc calculator should probably calculate the loading dose and make this clear and then the maintenence dose. i know there is a note re loading dose but i think when people use a calculator they just wait for the boxes to be populated and dont read the notes.

10. None
11. Having to go back to the beginning for each drug. Also, it might be appropriate if the calculated values stand out more clearly than the entered values

QUESTION 7

Please list the ideal properties of a dose calculator for patients in renal impairment (in order of priority)

1. --> ACCURATE --> WELL REFERENCED --> PEER REVIEWED --> GOO EVIDENCE BASE
2. by interval or use of pharmacokinetics methods
3. Fool-proof. Somehow can’t tick the wrong option in a drop-down list
4. Specifies the ClCr formula that has been used Consider all the dyalisis options Give references about the doses proposed (ex. if it is explained in the package information/Micromedex/Lexicomp/...)
5. Being able to enter the patients height and weight in either the metric or imperial system
6. Accurate Referenced with nomogram tables if possible Max doses (caps) Renal transplant patients Analysis
7. Easy to access, Quick to use For adjusted body weight it would be nice to be able to click on it to see the definition.
8. Accurate easy to use can save dose calculation you made- so can recheck it later.

9. Reliable Easy to use Accessible

10. Inclusion of weight adjustments for IBW

11. Needs to be clear what is being calculated and why. i.e. calculate ideal bdy wgt from hgt and then calculate crcl from this. then use ideal or actual wgt for dose. etc. i think it should be laid out in a step by step fashion

12. Age, height, gender

13. Accurate Accessible Easy to use

**QUESTION 8**

**What additional functionality would you like for an online calculator like SQUD?**

- Calculate SEVERAL drug doses for ONE patient
- Send alert to ANTIMICROBIAL or RENAL team
- Reporting tool by Clinical Area for follow-up
- App for iPhone
- App for Android
- Other (please specify)
QUESTION 9

MANUALLY calculate the dose of gentamicin you would give for the following patient: Age 74 years, weight 130kg, height 176cm, sCreatinine 200micromol/l, gender = male. Write the DOSE and COMPLETION TIME in seconds. Repeat this process WITHOUT CHANGING YOUR MANUALLY CALCULATED ANSWER above, using http://www.squd.eu and the login details referred to in question 4 above.
<table>
<thead>
<tr>
<th>S.No</th>
<th>Dose calculated manually (mg)</th>
<th>Time to calculate manually (secs)</th>
<th>Dose calculated using SQUD.EU (mg)</th>
<th>Time to calculate SQUD.EU (mg)</th>
</tr>
</thead>
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<td>2</td>
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<tr>
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<td>180</td>
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<td>19</td>
<td>2000</td>
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### 7.3. Summary

From the summary, I can conclude that more than 50% of clinical staff utilise eGFR for calculating renal function. Most of the staff are not using any electronic calculators for calculating eGFR. When the SQUD application is given for trial purposes, more than 90% people are satisfied with the application. A test scenario was given to calculate the gentamicin drug dosage level manually as well with SQUD application. With manual calculation out of 11 responses 6 responses has taken more than 5 minutes to calculate the dosage level, whereas with SQUD the time taken by most of them are less than 60 seconds and also most of the dosages are accurate. By doing this survey we got to know the limitations of SQUD applications, which we can focus in our future work.

### 7.4. Conclusion

This chapter presents an overview of the SQUD working model, its current status and feedback from the potential users. The next chapter describes future work and limitations of this system and provides a conclusion to the thesis.
8. Conclusion and Future Work

8.1. Conclusion

This thesis focuses on the question of how technology can reduce certain medication errors in hospitals. The resulting system, SQUD, is a collaborative project between clinicians and the IT department of NUIG.

Whilst the original gentamicin drug dosage calculator represented the most important and urgent clinical problem, the knowledge was easily transferable to a much larger group of ‘problem drugs’. The positive feedback from developing the gentamicin calculator encouraged further research in the drug dosing area. After several months of research, the importance of accurate drug dosage calculations and its complexity in calculating for clinical staff became apparent. After a series of considerations, a high level architecture was designed which contained two parts. The first part is a framework where any number of drugs can be incorporated into the system. The second part is a user interface designed for different devices such as mobiles, PDAs and computers. These devices can retrieve all the information about the drugs, calculate the dosage levels and are readily available to the users 24/7.

Consultation with stakeholders was an important part of this process. This has been critical, as with the most complex drugs it is hard to find clinician consensus as to exactly how to dose a drug like gentamicin. SQUD allows for the application to be programmed irrespective of decisions made at a local level. It has proved to be a flexible solution that can accommodate variation in local policy. Thus, it supports in meeting my primary research objective to lower and/or prevent medication errors. It also incorporates an internal reporting and messaging system for auditing the drugs and dosage levels. Whilst this approach may be at the expense of true global standardisation, local standardisation seems a far safer approach to the ad-hoc doses pharmacists use.

This research has been presented in 2 international conferences, 2 national conferences and 2 NUIG research days. Please see chapter 10 for details.
8.2. Future Work

This application has a lot of scope to be extended for future work. The following key points for future work include:

- Provide a 1-to-many functionality, so that by entering demographic data once many drug calculations can be accessed using a single click user interface.
- After the successful completion of the trials, SQUD will be made available to other clinicians and hospitals.
- Extend this research to other medications.
- Migrating to cloud based service to handle more users in a cost effective mode.
9. References


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10. Publications

1. A Multi-Platform Medication Support System for Clinical Use
   NUI-UL Research Day, April 2011, Galway

2. Beam me up Scotty - I’m on Gentamicin
   Hospital Pharmacists Association of Ireland: Annual Educational Conference, April 2011, Dublin

3. Right Dose, Right Care, Every Time – A Distributed System for Quality Use of Drugs.

