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Towards Improved ADR Reporting and Reports

A closer look at the quality of symptom description in the ADR reporting context

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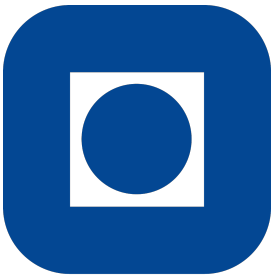

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Masters Thesis

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Preface

This report is written by Shahila Retnadhas and Yehonathan Raphael Quartey as part of their masters thesis "TDT4900 - Computer Science, Master's Thesis". This project is based on the ideas that arise from the specialization project done by us during autumn 2015.

Hereinafter 'we' refers to the authors of this master's thesis.

Acknowledgment

We would like to thank Associate Professor Øystein Nytrø for his guidance and feedback throughout the project. We would also like to thank him for the freedom given to us to explore and research in the field of our choice and for the motivation and inspiration to try and come up with possible solutions.

Our gratitude also goes out to the Pharmacists and Nurses at St. Olav Hospital for their support in this research.

We would also like to thank our friends and families for their constant moral support and motivation.

Abstract

Adverse drug reactions (ADRs) are considered as one of the leading causes of death among hospitalized patients and hence reporting such event have become crucial in recent times. Spontaneous adverse drug reaction reporting form (ADR forms) which can be electronic, paper based or both is an essential component and a major tool for pharmacovigilance systems in many countries. A significant portion of ADR reporting is patient's symptoms description which informs medical practitioners toward useful diagnosis. Symptoms description are usually in free text and as such have no identifiable structure. We research into adding structure and thereby improving the medically relevant information content of symptoms.

The objective of the study was to identify the possible ways to improve the quality of the ADR reporting with a special focus on improving the aspect of ADR reporting that has to do with symptoms descriptions.

Our approach included a research into the ADR reporting and symptom description domain which lead to the the development of a quality assessment model and the further development of a quantitative assessment method for measuring the completeness of symptom descriptions in the ADR context. The research also subsequently led to the development of a fill-in-the-blank prototype for symptom description which was intended improve upon the areas where the free-text input method failed.

In our experiments and analysis of data received from surveys conducted, we find that the content of symptom descriptions typically collected via free text are often incomplete. However despite the limitation of our fill-in-the-blanks approach it improves the completeness of symptom descriptions. We conclude that the contribution of our techniques adds value to the ADR reporting process.

Contents

List of Tables

List of Figures

CHAPTER 1

Introduction

Adverse drug reactions (ADRs) are considered as one of the leading causes of death among hospitalized patients. Thus monitoring of adverse drug reactions (ADRs) through pharmacovigilance is vital to patient safety. Spontaneous reporting of ADRs is one method through which pharmacovigilance serves this monitoring purpose and have become an important phenomenon. Spontaneous Adverse Drug Reaction reporting forms, which can be either electronic, paper based or both, are an essential component and a major tool for pharmacovigilance systems in many countries. This form is a tool to collect information of ADRs which helps in establishing the causal relationship between the suspected drug and an adverse reaction or event [2].

Adverse drug event reporting forms, whether electronic or paper based, contain fields that allow users or reporters to express adverse events or reaction in detail. Due to the fact that reporters vary in language and expressiveness, data collected via free text end up being inconsistent and lack an easily identifiable structure useful for information extraction. This introduces a large amount of unstructured free text into the system. The usefulness of structured data that can be formally read and understood by computers cannot be overlooked. We look at controlled language for the free text portions of ADR reports; thus symptom description for adverse event reporting. This is a proposed step toward a broader method for implementing a guided-reporting system which can intelligently guide free text to conform to a formal language in real time.

While some research and approaches to adverse event reporting has been about how to automatically analyze and extract relevant information from free text reports [11], we on the other hand focus on the reporting side of the domain and research toward finding out possible ways to improve the quality of the ADR reports through the reporting process. Symptoms Descriptions is an example of information that is

collected from ADR reporters through free text submissions. In this thesis, we narrow our focus to symptoms description and assess the quality of descriptions based on a novel AC3 Quality Assessment Model.

1.1 Problem Statement

There are different means of submitting an Adverse Drug Event report and these include through e-forms, manual forms, telephone, fax, email etc. However, the most common ways that ADRs/ADEs are submitted are through electronic and paper-based forms. The nature of these form fields encourage the input of free-text. The information thus entered are usually not machine readable and this is a disadvantage in that, the extraction of valuable information such as DDIs etc. from these free text fields are more difficult compared to other input fields that support semantics and are accompanied by named drop-down and selection fields. In this work, we research into the completeness, consistency and accuracy of ADR reports and explore the possibility of introducing controlled language into the ADR reporting domain with a narrowed focus on side-effect or symptom description.

Symptoms are normally sensations, feelings, bodily functions, activities or behaviors [12]. Symptoms description is a vital part of drug adverse event reporting, it captures the user's expression of their symptoms that they experienced from drugs they take. However patients often fail to provide the details necessary to effect useful clinical decisions. This can be partly attributed to the fact that most patients do not know exactly what is required in a symptoms description and even if they do, they may need a formal guide to help get the most relevant and detailed information out of them.

1.2 Background and Motivation

The development and use of new drugs to mediate illness has had its advantages and disadvantages in recent times. Clinical trials are done with a smaller group of restricted people for a defined time. However, the person-to-person variability to drug responses is one of the main problem in the clinical practice and drug development that leads to adverse effects of drugs in patients [13]. This makes it too difficult to find all the possible adverse reactions and side effects of the drugs before they are made available for patients use [14]. Muehlberger et al. reviewed 25 studies on ADR

frequency from the past 25 years and estimated the frequency of ADR.

According to their study, the studies on selected high-risk patients and those spontaneous reporting are of lower ADR proportions (2.9% and 2.5%). Studies among patients admitted to hospital are higher in proportion. On an average 5.8% of all hospital admissions to medical ward have been shown to be due to adverse drug reactions. The lower and upper proportions for the same is 2.9% and 2.5%. It is therefore imperative to continuously monitor the effects of the drug on the patients in order to identify possible adverse reactions and drug interactions [15].

Adverse Drug Reactions Reporting Systems as generally referred to in this report are the spontaneous reporting systems for reporting drug safety problems identified post-marketing. This is the main data source for pharmacovigilance and relies largely on the clinicians and/or the patients to report about the adverse drug reactions that they suspect could be of a particular drug. However various studies indicates that there is still under-reporting of ADRs [16, 17]. One of the main factor that contribute to under-reporting is the time constraints on clinicians. A number of other studies have focused on spontaneous reporting of ADRs and highlighted patient reporting in contrast to reporting done by practitioners. Some of the issues that come up in a recent survey was that suspected ADRs reported to GPs were not then passed on to the regulatory authority, or even recorded in medical records. Accordingly, the Netherlands patient reporting scheme also showed that patients report a suspected ADR when they consider that a health professional has not paid attention to their concerns [18].

A report by Health Action International, an international non-governmental organization that is entirely dedicated to strengthening medicines policy to improve public health, indicated that patients provide much more detail and clearer descriptions of their experiences than health professionals when reporting suspected ADRs, indicating a desire to explain their experiences [19]. This makes it clear that it is important for the patients to be able to report the suspected ADRs. It is no doubt that spontaneous patient reporting is important if any progress is to be made in this respect, yet the usefulness of reports by health practitioners is equally useful. While a report from a patient may be more descriptively detailed, that from a health practitioner is likely to be more technically detailed as well. However there are difficulties a patient may face regarding understanding and providing details like medical terminologies and ICD codes. These data can be provided by the physicians if the suspected reaction is reported by them.

Therefore to look at both reporting parties in a competitive and contrasting view may not be the best approach in looking at reporting of ADRs. A workable suggestion is to combine the reports of practitioners with that of patients in order to produce a more holistic report that captures both a descriptive and technical depth. It can be argued that if both practitioners and patients report on the same ADRs then reports will have a more quality depth of information. Studies have shown that a significant number drug adverse reaction cases are as a result of drug to drug interactions [20]. Practitioners can state suspected drug to drug interactions when reporting ADRs.

Though there exists a large amount of data on ADRs now, it is not fully used as the quality of the reports are not good and it is difficult to extract the necessary information needed from the reports. A significant part of research on Drug Adverse Events and Drug-Drug interaction borders around the analysis of retrospective data and the attempt to extract semantics from said data [11, 21]. It is however worth arguing that if more attention was given to the reporting process of ADR and subsequent DDIs, the identification and prevention of such reaction will be easier remedied. In this project, we do a literature study on adverse drug event reporting and try to explore how the reporting process can be made more interesting and interactive, study ways that the time taken to report can be significantly reduced, and possibly improve the quality of report content.

1.3 Research Goals

The aim of the research is to explore possible improvements to ADR reporting and reports. Does the introduction and implementation of controlled language for medical terminology in the ADE reporting forms improve the quality of the reports submitted by the patients with respect to the completeness, correctness, consistency and adequacy of reports specifically symptom descriptions. We identify the following sub goals as part of our overall goal toward and improved ADR reporting.

G1: Research on the state-of-the-art of the symptom description. The goal is to learn about research done on symptom description and form a knowledge base to support our assessment of the domain.

G2: Develop a quality assessment model based on the following quality indicators; completeness, consistency, correctness and adequacy. Here we aim to assess sample symptom descriptions based on the ear-

lier stated model and draw conclusions form the results we obtain.

G3: Explore the introduction of controlled language into the symptom description domain and assess its effect on the quality of reports with respect to the earlier quality model. Controlled language here comprises both controlled English and controlled vocabulary. We implement controlled vocabulary by introducing auto-completion and suggestion of medical terminology into the symptom description reporting process.

We primarily seek to answer the following questions:

- Is there an improvement in the completeness of the reports?
- Are the reports more consistent than the reports submitted through the existing form?
- Is the information more accurate than the information captured through the existing ways?
- Does it help the reporters to report accurately their symptoms and also reduce the time taken to submit?

1.4 Scope of work

The area of pharmacovigilance that has to do with ADR/ADE is quite vast and stretches from pre-reporting processes to reporting processes to report data to post-reporting processes; not to mention everything in between. We therefore focus on the reporting aspect of this domain and consider improvements to the reporting process as well as the subsequent data collected. Here we deal with free text reporting and research into controlled language for free text reporting; specifically symptoms description, but not limited to.

1.5 Operational Definitions of Terms

ADE

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, of which the U.S. Food and Drug Administration (FDA) and the World Health Organization are members, defines an adverse drug event as "any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment" [22]

ADR

The term adverse event is not particularly helpful to physicians, but it provides context for the more clinically useful term adverse drug reaction. The International Conference on Harmonisation defines an adverse drug reaction as "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function" [22].

Spontaneous Reporting

Spontaneous reporting is the reporting of the suspected Adverse drug reactions by the health-care professionals, manufactures, nurses, pharmacists or patients. They are called spontaneous because the reporting takes place during the normal diagnostic appraisal of the patient and the clinician suspect the drug for the adverse event. It is important to report the serious and previously unknown suspected ADRs [23].

Controlled Language

Controlled natural languages (CNLs) are subsets of natural languages that are obtained by restricting the grammar and vocabulary in order to reduce or eliminate ambiguity and complexity. The need for controlled natural languages arise due to the inherent ambiguities that come with all natural languages. In order to formalize a language thus make it machine readable, there is a need to eliminate these ambiguities. This brings about the necessity for controlled language. [24]

Pharmacovigilance

Pharmacovigilance (PV) as defined by WHO "is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" [25]

Symptoms

A symptom is described as "any change in the body or its function that indicates the presence of disease" [26].

Drug-Drug Interaction

Drug-Drug Interactions (DDI) is a situation in which the effect of a drug is altered when it is interacted with another drug. This could alter the way the

drug (one or both) acts in the body and/or may cause adverse side effects [27].

1.6 Report Structure

In this report, we start of with an executive summary in the form of an abstract which gives a brief preview into the scope of our work. The rest of the thesis is organized as follows. We introduce the thesis in Chapter1 and state our goals. Chapter2 presents the background information of the whole clinical process and the Adverse Drug Reporting. In Chapter3, we presented the existing studies that have been done on the improvement of the quality of the ADR reporting and ADR reports. We also presented the state-of-the-art of the ADR reporting and the studies related to symptom description.

In Chapter4, we talk about the methodologies we employed in our research. We also present our novel AC3 quality model for evaluating the quality of ADR reports as a child of the research done in this chapter. Chapter5 talks about the implementation of a prototype system and the plan to conduct a usability test. Chapter6 deals with the experimentation, results and discussion. In Chapter7, we write the conclusion based on the results of the experiments and provide some recommendations in that regard. Finally in chapter8, we write about some future works that can be done to contribute toward the improvement of our work and the realization of our goal.

1.7 Documentation & Collaboration Tools Used

This project is a collaborative project and we decided to use the following tools for easier collaboration.

Google Drive

Google-drive is a web-based tool which is free and allows users to store, edit and share the files/documents with anyone. It consists of GoogleDocs, GoogleSheets, GoogleSlides and more. Everyone has access to it and it makes the real-time collaboration easier. We can edit the documents simultaneously at real-time and also share the documents with the supervisor for review [28].

Facebook

Facebook is a social media connecting people which helps in non face to face communication between us. We interact through facebook to discuss some

ideas and thoughts related to the project. We also share information such as rooms for our meeting, interesting links related to our project etc [29].

Zotero

Zotero is research tool that helped us to organize the articles and other sources of information we referred during our research process. This is the main tool which we used for our research method. We searched the different databases for the identified keywords and used the zotero plugin to organize all the screened articles. This made us easy to identify the duplicates and eliminate the duplicate sources [30].

Overleaf

Overleaf is an online editor for collaborative writing of research reports in LaTex. Overleaf is free and easy to use. We write the report in the left part of the editor and we see the preview of the report at the right side. The program is compiled as we edit the document and display errors if any immediately which helps us to correct immediately [31].

CHAPTER 2

Background Theory

In this chapter we present some of the concepts in the domain of adverse drug reporting. These theoretical concepts capture the reasons, processes, pre-processes and post processing for ADR/ADE reporting and are relevant toward the further understanding of the domain.

2.1 Historical Background

Drug disasters holds an important place for the awareness of ADRs. The thalidomide tragedy lead to the development of drug regulation safety requirements and to the introduction of spontaneous reporting of ADRs across the world.

2.1.1 The Death of Hannah Greener

Drugs may have an effect on human beings other than the ones intended and this fact has been known for many years. On the 29th of January 1848 a young girl , Hannah Greener, was given chloroform, an anaesthetic which had only been introduced a year earlier, before treatment for an ingrown toenail. Unfortunately Hannah died during the anesthetic from what was thought to be an episode of ventricular fibrillation. As a result of public and professional concern of over the safety of anaesthetic, the incident received wide publicity. The Lancet journal set up a commision which invited doctors all over Britain and its colonies to report anaesthesia-related deaths and the results were published in 1893. This was the forerunner of spontaneous reporting system for suspected adverse drug reactions but unfortunately the system of reporting anaesthesia-related deaths was neither retained or extended to other drugs until after the thalidomide tragedy in 1961 [32].

2.1.2 The Thalidomide disaster

Thalidomide was first developed in Germany in the year 1954 and was made available to patients from 1957. This was the post-war period during which the world was addicted to sleeping pills and tranquilizers. Thalidomide was described as the "wonder drug" and were prescribed for safe and sound sleep. The developers advertised the drug as completely safe for pregnant as well as feeding women. The sales of the drug almost reached those of Aspirin in 1960 [33, 34].

Dr. William McBride, an Australian obstetrician found that the drug also relieves nausea and vomiting due to morning sickness and started suggesting the drugs to his pregnant patients. He found severe birth defects in the babies he delivered in 1961. Upon researching he found that there is a connection between the so-called harmless compounds and the babies born with birth defects. The drugs get in the way of normal development of the babies and were born with *Amelia* (absence of limbs), *Phocomelia* (absence of most of the arm with hands extending flipper-like from the shoulders),*Dysmelia* (malformation, missing or extra limbs) like the kindergartner pictured below. [14, 17]. Many children born during that period had this serious adverse effect due to the drug Thalidomide taken by the mothers during pregnancy.

Figure 2.1: Children from Dovecot County Primary School affected by Thalidomide [2, 3]

The drug has been introduced again in the recent years to treat many new conditions such as the treatment of inflammation associated with Hansen's disease (leprosy) and as a chemotherapeutic agent for patients with multiple myeloma. The System for Thalidomide Education and Prescribing Safety

(S.T.E.P.S.) program designed by Celgene pharmaceuticals controls the use of the drug in patients and also educate about the harmful effects of the drug to the patients receiving the drug [2, 33].

2.1.3 Drug Safety Monitoring

The Thalidomide Tragedy, stimulated national and international action towards ensuring the safety of drugs and reducing the risk of adverse reactions to said drugs. The drug approval are made rigorous and there started the beginning of the various monitoring systems today in the world.The World Health Assembly, the supreme decision making body for the World Health Organization (WHO) reacted to this strategy by initiating and international system of drug safety monitoring and led to the cooperation between the pharmaceutical industry and drug regulatory authorities working together to monitor and control potential drug adverse reactions [33, 35].

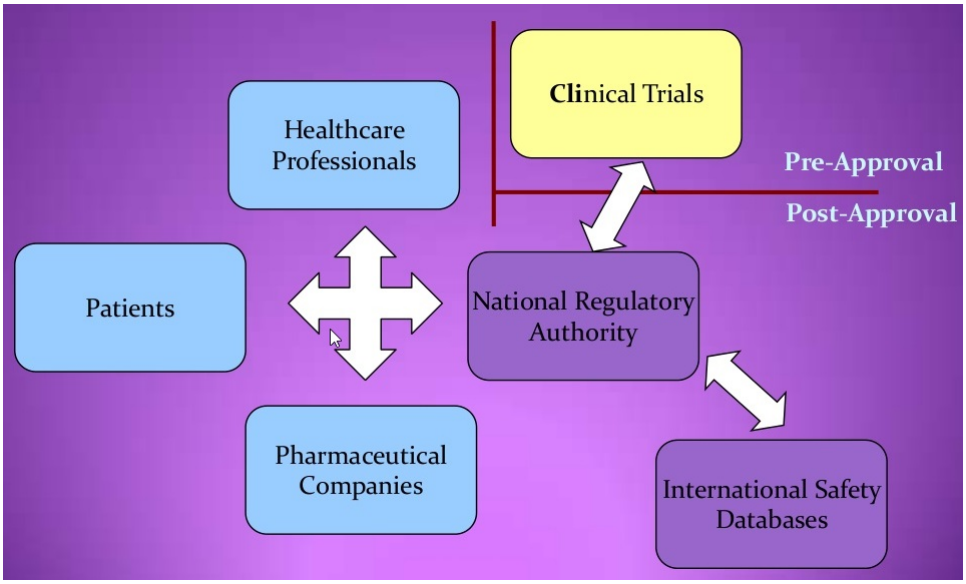

Figure 2.2: System of Safety Data Gathering [4]

Globally, national pharmacovigilance systems rely on spontaneous or voluntary reporting in which suspected adverse drug reactions (ADRs) are reported to a national coordinating centre by health professionals, manufacturers or patients. Spontaneous reporting systems are the easiest to establish and the cheapest to run but suffer from poor quality reports and under reporting. It is difficult to estimate rates and frequencies of ADRs through spontaneous reporting [36]. The most common way that regulatory

bodies collect ADR information for medicines once they are on the market is through voluntary, spontaneous reporting structures [9]. Figure 2.7 shows a flow diagram that proposes when an ADR is required to be reported.

Clinical trials, which involves testing the safety of a drug on humans has a number of limitations including the following [9, 37]:

- Trials usually involve homogeneous sample population
- Most trials assess relatively healthy patients with only one disease and mostly exclude specific groups such as pregnant women, children and the elderly
- Small sample sizes reduce the chance of finding rare adverse effects
- Trials last for a limited duration and hence preclude the discovery of long-term consequences
- Drug interaction can be substantial in a population as patients may take drugs concomitantly and this can almost never be predicted by clinical trials.

Due to the limitations of clinical trials when a drug is first marketed, much may be known about its efficacy whereas relatively little may be known about its safety, at least 30,000 people need to use a medication in order to identify, with 95 per cent power, an adverse reaction with an incidence of one in 10,000.8 A relative lack of widespread clinical trials for medicines to treat children means that many drugs are initially only licensed for use in adults, which can leave no alternative to the prescriber than to use "off-label" and unauthorized products in this population. Therefore, the need for post-marketing surveillance can be seen as a means to identify drug safety problems not picked up by pre-marketing tests and advise prescribers and users [9]

2.2 Clinical Research

When a drug is discovered and synthesized anew it undergoes toxicological and pharmacological tests in animals, followed by clinical trials in humans. The pre-clinical research conducted to prove the underlying research hypothesis (explain how the new treatment works) in a laboratory, although answers basic questions about how safe a drug is for use, is not a suitable substitute for studies of ways in which the drug interacts with the human

body. Clinical research refers to studies, or trials, that are done in people to further ascertain a drug's safety. Designing the clinical study involves considering what is to be accomplished for each of the different Clinical Research Phases. The Investigational New Drug Process (IND) refers to the process clinicians must go through before clinical research begins [34].

Researchers design clinical trials to answer specific research questions related to a medical product. These trials follow a protocol, a specific study plan developed by the researcher or manufacturer. Researchers review prior information about the drug to develop research questions and objectives, before a clinical trial begins. Figure2.3 shows the different phases and timeliness of a Drug Development Process. In doing so they decide the following:

- Selection Criteria: Who qualifies to participate
- Number of Participants: How many people will be part of the study
- Length of Study: How long the study will last
- Limiting Research Bias: Using a control group or other ways
- Drug Administration and Dosage: How the drug will be given to patients and at what dosage
- What assessments will be conducted, when, and what data will be collected
- Review and Analysis of Findings: How the data will be reviewed and analyzed

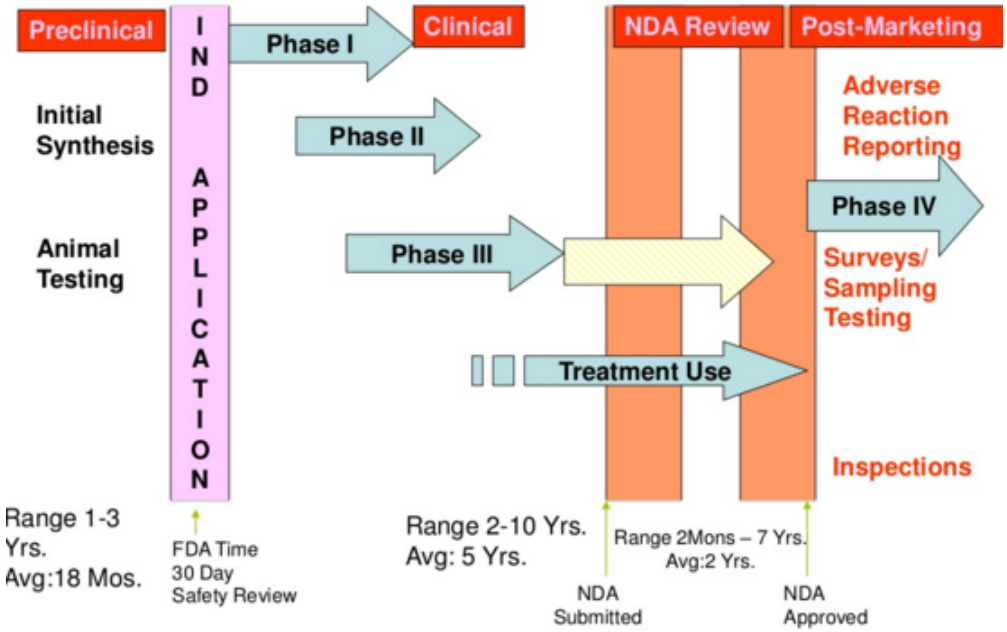

Figure 2.3: Drug Development Process [5]

A resource from cancer.net [36], describes the phases of clinical trials for drugs for cancer patients according to the US Food and Drug Administration regulations. Clinical trials follow a typical series from early, small-scale, Phase 1 studies to late-stage, large scale, Phase 3 studies.

2.2.1 Phase I Clinical Trials

The goal of a phase I clinical trial is to show that a new drug or treatment, which has proven to be safe for use in animals, may also be given safely to people. Doctors collect data on the dose, timing, and safety of the treatment. People who participate in phase I clinical trials are often the first to receive a new therapy or a new combination of therapies. In this phase, dosage are increased gradually to find the dosage that works best without severe side effects.Trials last several months to a year and most often involve a small number of people, usually no more than 10 to 20 [36].

2.2.2 Phase II Clinical Trials

Trials provide information about the safety of the treatment in more detail as well as evaluate how well the drug works. The focus of the this phase is to find out whether the new treatment works for a specific cancer. Phase II clinical trials take about two years to complete and usually involve about 20

to 40 people. The new treatment needs to show it is likely to work and is safe when compared to the standard treatment for it to be tested in phase III clinical trials [36].

2.2.3 Phase III Clinical Trials

In this phase the new treatment that has shown promising results when used for a small number of patients with a particular disease is compared with the current standard of care for that specific disease. Data are gathered from large numbers of patients to find out whether the new treatment is better and possibly has fewer side effects than the current standard treatment.Although phase III clinical trials focus on patients with a specific disease, they typically include patients of various ages, ethnicities, and both genders so that the results may be applicable to a large number of people [36].

Although the pre-marketing investigation, preclinical and clinical trials, of a new medicinal product is carefully performed and critically assessed, it does not always reveal all possible effects, side-effects or adverse reactions due to the fact that there are multiple potential new co-factors of real life, cannot be replicated in clinical trials. The introduction of a new medicinal product, therefore, always carries unknown risks, as numerous instances during the past decades have demonstrated. In this situation the alertness of the prescribing physician and the quality of the operational system for reporting adverse reactions are crucial. [34]

2.2.4 Phase IV Clinical Trials

Phase IV trials are the safety surveillance in real-life patients post-marketing of the drugs. This phase is to detect any rare serious or long-term adverse effects that were not identified during the earlier trials. If any serious effects are identified in this phase, it could lead to cancellation of the drug licence and no longer being sold or restricted use [2].

2.2.5 Involved Parties

Clinical research takes place in a network consisting of different parties and collaborations. The different parties involved in the Clinical research process are,

- Sponsor
- Investigators and monitors

- Subject
- Contract Research Organization(CRO)
- Ethics Committee
- Regulatory Authorities

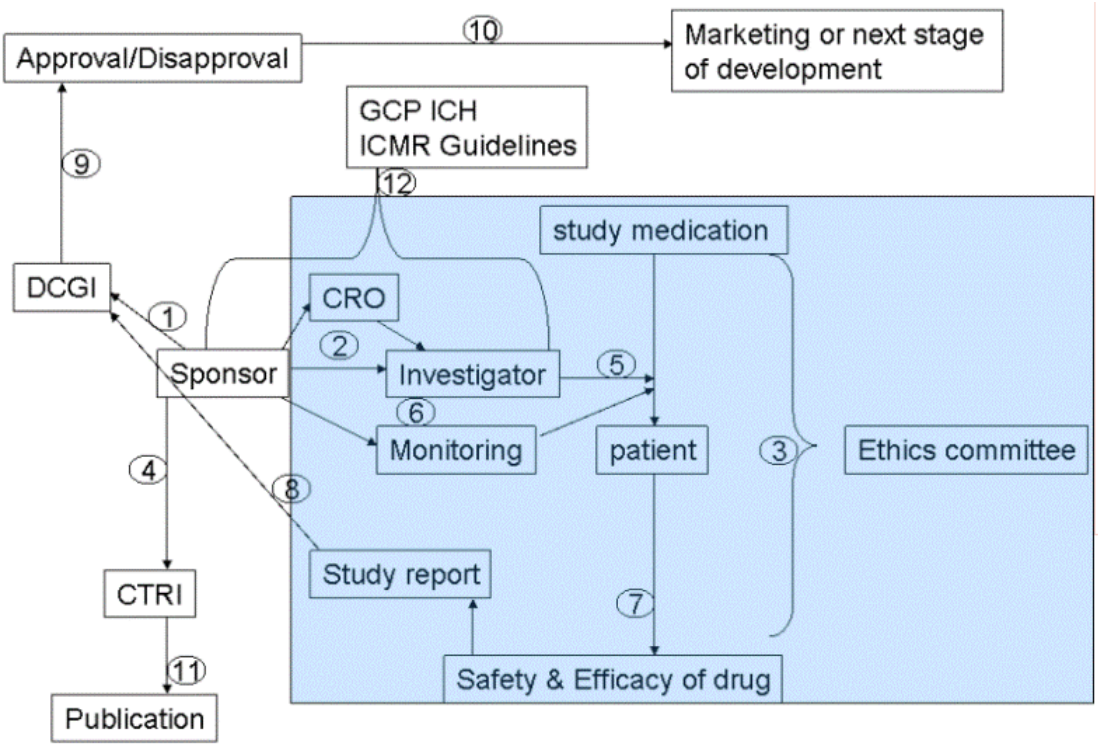

Figure 2.4: Flow chart and interactions of various parties involved in clinical research [6]

Each of the above internal/external parties have their own roles and responsibilities in the clinical research process. Figure 2.4 shows the different parties involved in Clinical Research in India and their flow and interactions.
Below is the detailed explanation of the steps and the interactions between the different parties [6].

1. The first step of the process starts when a sponsor decides to conduct a research. The sponsor prepares all necessary clinical trial documents such as protocol, case record form, investigator's brochure, patient information document and informed consent form, etc. The qualified

investigators and monitors are also identified by the sponsor. The sponsor then applies to DCGI (Drug Controller General of India) seeking permission with all the documents and some more information.

2. After getting the permission from DCGI, the sponsor sends all the documents to the investigators for further process.

3. The investigators forwards these documents to the ethics committee and waits for their approval. The main concerns of ethics committee are safety and rights of the participants (patients) and review the protocol from this point of view.

4. The sponsor then registers the clinical trial in the clinical trial registry of India. Registration after getting approval from the Ethics committee.

5. After the approval of all the above regulatories, the investigators start the patient recruiting process as per the criteria defined in the protocol. The authorities then give an study medication to the selected patients.

6. The sponsor sends the monitor to observe the trial process and checks whether it is conducted as per the protocol.

7. The investigation results are captured in the case record form by the investigators.

8. The observation collected are analyzed after the completion of the study to find the safety and efficacy of the drug investigated. The detailed study report prepared by the investigators are then submitted to DCGI

9. DCGI approves/disapproves and grant/deny permission for further development of the drug. It may also ask to repeat the trail.

10. The drug are marketed after DCGI approves the phase III report of the product.

11. Sponsors/Investigators publish the trails (positive and negative) in the journals.

12. All the above activities should follow the clinical practice guidelines by ICH and ICMR(Indian Council of Medical Research).

2.3 Pharmacovigilance

Pharmacovigilance (PV) as defined by WHO "is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" [25]. Pharmacovigilance is a vital part of clinical research process. PV is the process by which the adverse drug events related to the drug, that are identified both during the drug development process and post-marketing are received, reviewed and assessed.

A separate system for identifying the adverse events post-marketing is maintained in order to identify the safety concerns not deleted during the drug development process. The pre-marketing clinical trials are carried out on limited number of patients for a short duration of time with controlled conditions. There can be many things that were not identified during the pre-marketing trials such as rare but serious adverse drug events, reactions due to the patient's different geographical conditions etc. This leads to the conclusion that the pre-marketing clinical trials are not always complete. Post-marketing, the drug use needs to be monitored continuously due to the following reasons:

- There can be an unexpected adverse reaction happened that was not identified during the pre-marketing clinical trials
- The effects of the drug can be affected due to patients having more than one disease and taking many medicines.
- The drug are used in the general population with many differences between the people like geographic location, medical history, age, gender etc.

The main aim of PV is to identify the unknown safety problems as early as possible and prevent patients from being affected by then unnecessarily. The importance of pharmacovigilance is that it helps to improve the patient care and their safety with respect to drug use and all medical and paramedical interventions. It also helps in assessing the risk, harm, benefits and effectiveness of drugs and mitigate the risks earlier as possible in the drug development [25].

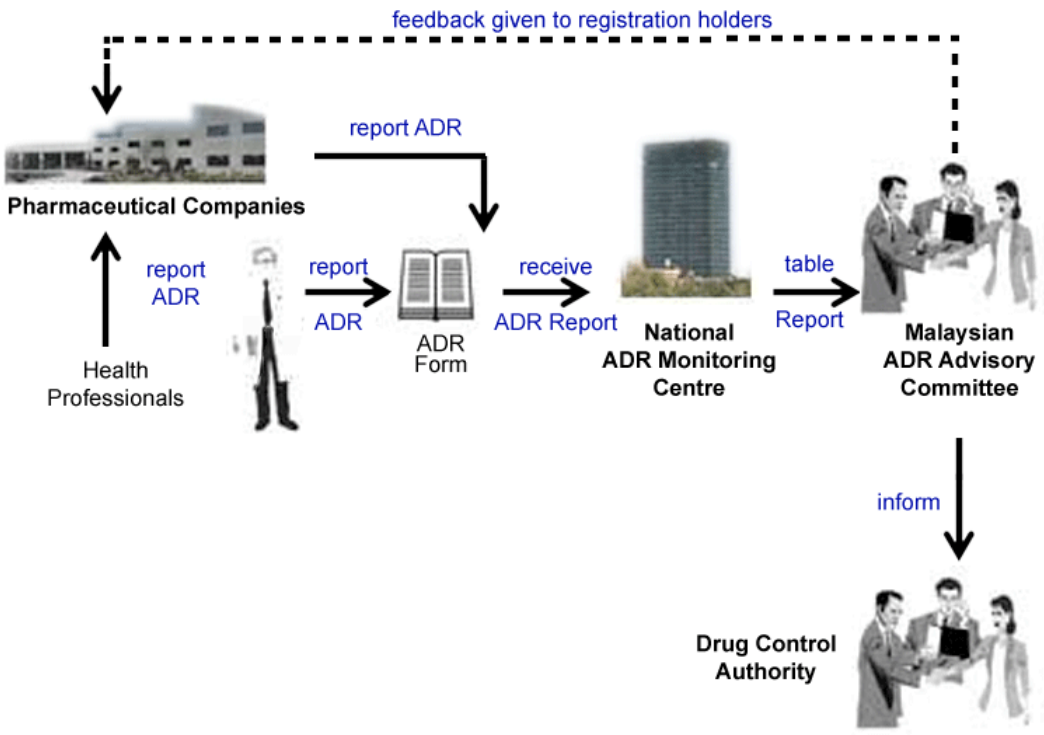

Figure 2.5: Malaysian ADR Reporting mechansim [7]

The collected ADR reports are assessed for data completeness, seriousness, relatedness and expectedness which are the responsibilities of PV. The reports are then sent to the pharmaceutical company responsible for the drug and also to the national monitoring committee. The safety of the medicine are then evaluated against the reported adverse event and the feedback is sent to both the company and the drug control authority. Based on the new information provided to the drug control authority, it can be either stopped from further use or restrict their use. Figure 2.5 and Figure 2.6 shows the malaysian and US flow of information and sequence of action on the submitted ADR reports respectively [7, 8].

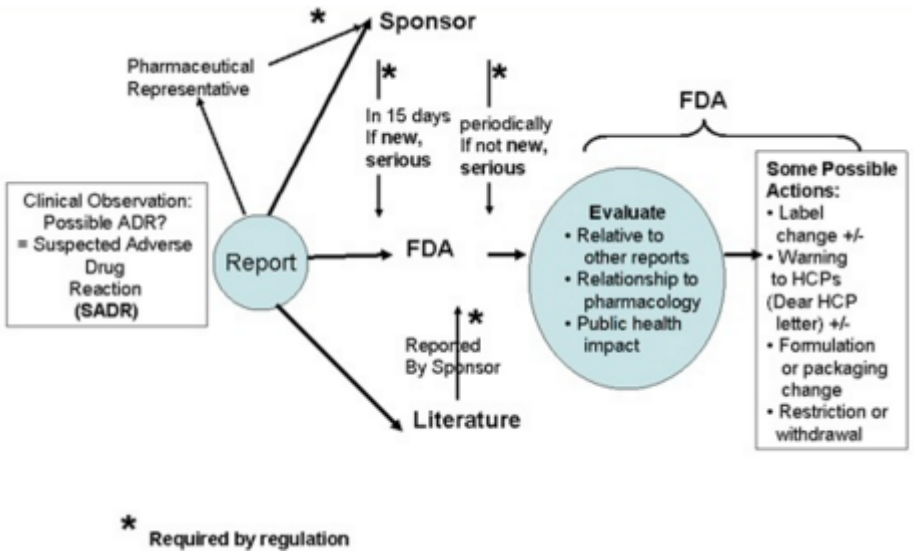

Figure 2.6: Flow of information and actions on a suspected adverse drug reaction report (SADR) [8]

2.4 Adverse Drug Reactions

The term adverse event is not particularly helpful to physicians, but it provides context for the more clinically useful term adverse drug reaction. The International Conference on Harmonisation defines an adverse drug reaction as "a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function" [22].Figure 2.7 shows a flow diagram that proposes when an ADR is required to be reported.

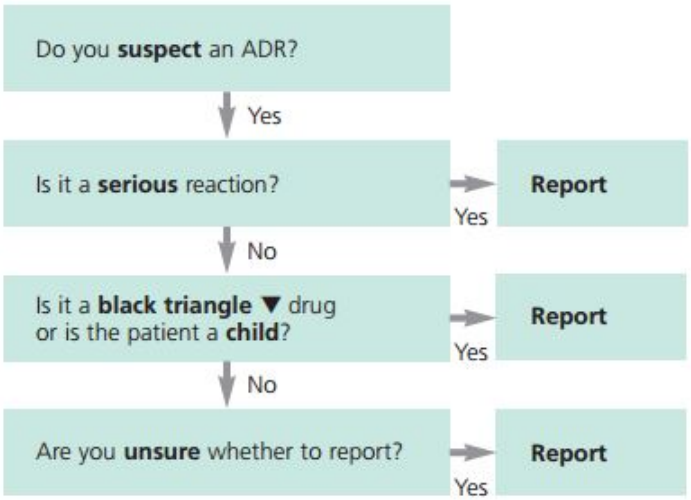

Figure 2.7: Flow diagram to show when an ADR must be reported [9]

2.4.1 Classification of ADRs

ADRs are classified based on the distinction between the dose-related and non-dose related adverse drug reactions. This is the most common method of classification of ADRs [1].

Type A

The dose-related ADRs are called "type A - augmented effects of the drug action". Type A ADRs are the most common type constituting over 80% of the overall ADRs. This results from the pharmacological action of the drug and are predictable from known pharmacology. These are mostly mild ADRs and are managed by reducing the dose or stopping the use of drugs.

Type B

The non-dose-related ADRs are called "type B - bizarre reactions". Type B ADRs are not very common and are just the opposite of type A, that is they are not related to the pharmacological action of the drug and are not predictable. Though there are variable severity, they are considered more severe than the type A ADRs. These types of ADRs are managed by withholding and avoid the use of the drugs in the future.

There are some more classification but they are considered as the subclasses or hybrids of type A and type B ADRs.

Type C

The type C ADRs are called chronic reactions which is a dose-and time-related. Type C ADRs are uncommon and are related to cumulative drug and long term exposure are required.

Type D

The type D ADRs are called delayed reactions, which is time-related. Type D is also uncommon and are usually dose-related. They are seen when the drug are used for a prolonged period of time or used during critical time.

Type E

The type E ADRs are called end of use reactions. These kind of ADRs occurs soon after ending the use of certain drugs and they are maintained by reintroducing the drug and withdrawing it slowly.

Type F

The type F ADRs are called failure of therapy reactions. These are common ADRs which are mostly dose related and are often caused by drug-drug interactions. These kinds of ADRs are managed by increasing the dosage or change in the therapeutic agent.

Table 2.1 shows some examples for each of the different types of ADRs as presented in the referred article [1].

Table 2.1: Examples of different types of ADRs [1]

Type of ADR	Examples
Type A	*Drug toxicity* • Nephrotoxicity caused by aminoglicosides • Dysrhythmia caused by digoxin *Side effects* • Constipation caused by chronic opioid use • Anticholinergic effects of tricyclic antidepressants
Type B	Intolerance • Tinnitus caused by small doses of aspirin Allergy (hypersensitivity or immunological) • Result of an immune response to a drug: Penicillin-induced urticaria
Type C	Hypothalamic-pituitary-adrenal axis suppression by corticosteroid
Type D	• Teratogenesis • Carcinogenesis • Tardive dyskinesia caused by antipsychotic medication
Type E	• Opiate withdrawal syndrome • Rebound hypotension on clonidine withdrawal
Type F	• Ineffectiveness • Resistance of a micro-organism or tumour to the drug action • Tolerance • Tachyphylaxia

2.4.2 Factors affecting the occurrence of ADRs

There are number of factors that influence the occurrence of ADR and are grouped into 5 categories:- Patient related factors, Social factors, Drug related factors, Disease related factors and ADR related factors [38].

1. **Patient related factors**

   - **Age :-** Age is an important factor influencing the ADR. Elderly and pediatric patients are more susceptible to ADRs as the

drug absorption and metabolism varies more across these group of people.

- **Gender :-** The biological difference between males and females like, body weight, body compositions, metabolism etc. affects the way in which the body reacts to the drugs.
- **Maternity Status :-** There are certain physiologic changes occurring to the body during pregnancy and may affect the way the body reacts with a particular drugs. Not only the women but also the fetus are exposed to the ADRs.
- **Fetal development :-** The fetal development plays an important role in the effect of drug. There is a difference on the effect of the drugs in each semester.
- **Creatinine clearance category:-** This refers to the function of the kidney which is responsible for many drug excretion. Kidney disease affects drug clearance and metabolism thus influencing the ADRs.
- **Allergy:-** The abnormal reaction of the immune system to a particular drug (often referred as Drug allergy) also sometimes cause an adverse event.
- **Body weight and fat distribution:-** When drugs are taken, they are distributed to/from the blood vessels and different tissues of the body. After the absorption of the drugs from the blood stream to different tissues, Some drugs dissolve in water, some stays in the blood-cells and the fluid around the cells and some dissolve in fat. The absorption and release of drugs into the blood stream has effect on the drug reactions. For instance, obese people may store large amount of fat-soluble drugs and are released slowly into the bloodstream. Thus the effect of the drug is prolonged. In thin people, the less amount is stored. In elderly thin people large amount of drugs are stored as the body fat increases with age.

2. **Social factors**

- **Alcohol drinking:-** Alcohol interacts with many drugs and affects the drug metabolism and changes the strength of ADRs making it more toxic and harmful to patients.
- **Race and ethnicity factors:-** The important demographic variable that contributes to the inter-individual variability in metabolism and response to medication is ethnicity. Ethnic background is greatly related to the genetic factors and studies discuss

that it can determine one's susceptibility to both Type A and Type B ADRs.

- **Smoking:-** One of the risk factor related to many diseases is Smoking. Smoking affects the liver enzymes and affects the metabolic process resulting in a decrease pharmacologic effects.

3. **Drug related factors**

   - **Polypharmacy:-** Patients suffering from many disease consults different doctors and are exposed to different drugs. ADRs may occur due to drug to drug interaction.
   - **Drug dosage and frequency:-** The frequency and the drug dosage might have a serious effect if they are not taken properly (eg.overdose if not taken at proper intervals). For example, some drugs are to be taken in the morning, some in the evening and some before bedtime.

4. **Disease related factors**

   Patients disease has high influence on an ADR. If the patients have more disease, it makes them more susceptible to ADRs. Several disease in a person is also one of the factor which cause drug-disease interaction and ADRs.

2.4.3 ADR Reporting Stakeholders

There are many participating parties to the area of pharmacovigilance involving adverse drug reaction reporting. These stakeholders are those who are involved and/or will and do benefit from the furtherance of the area.

Patients

Patient health is of paramount importance and issues of health in some cases is a matter of life and death. Drug are made for human beings and therefore these individuals whose lives are concerned hold perhaps the highest stake in the matter of adverse drug reaction reporting. Reporting of a suspected ADR in a patient can help identify any allergies/side effects they possess towards a drug and helps them avoid their exposure to the drugs in future depending on the severity of the reaction of course.

Healthcare professionals

Reporting an ADR helps the healthcare professionals prevents the possible adverse effects happening from the similar group of patients having the similar case history. Health professionals in their occupation, are responsible for the health of their patient and are therefore concerned with the drugs with may threaten this health. Since they deal directly with the patients, the onus lies on them to detect and report on these adverse effects according to their discretion.

Pharmaceutical industry

As this industry is responsible for coming up with drugs, any resulting side effect falls within their responsibility. ADR reporting helps the pharmacy industry to monitor the safety of the drug use across people, continent and avoid serious events happening to people.

Nation & Global Concerns

There are national and global concerns that the issue of adverse drug reaction pose. The health of the people in a nation or even the world as a whole has a direct bearing on the economic and social development globally. Adverse reactions are everyone's concern due to the fact that a disease outbreak in one area can easily spread to another. Countries must spend lots of money on health related cases and even a lot more when adverse reactions are concerned.

2.5 Spontaneous ADR Reporting Systems

This section introduces examples of spontaneous or voluntary reporting systems currently being used in some countries to report adverse drug reactions(ADR) and/or adverse drug events(ADE). These report systems are deemed spontaneous because they depend on the discretion of the reporters. The link to some countries ADR forms are given in Appendix A

2.5.1 US Food and Drugs Administration

The US Food and Drugs Administration is a federal agency of the United States Department of Health and Human Services responsible for protecting and promoting public health through the regulation and supervision of food safety, tobacco products, dietary supplements, prescription and over-the-counter pharmaceutical drugs (medications), vaccines, biopharmaceuti-

cals, blood transfusions, medical devices ,electromagnetic radiation emitting devices (ERED), cosmetics, animal food and feed and veterinary products. They provide an online form for reporting serious adverse events related to human medical products, including potential and actual product use errors, product quality problems, and therapeutic inequivalence/failure [10]

2.5.2 British Yellow Card Scheme

The British Yellow Card Scheme is a spontaneous or voluntary reporting system for reporting the suspected problems or incidents in pharmacovigilance. It was developed and is run by the Medicines and Healthcare products Regulatory Agency (MHRA), an agency of the Department of Health in UK. Reports on suspected reactions can be submitted by physicians or patients, on any medicines available in the UK market for patients use, including side effects to vaccines, herbal medicines, and homeopathic medicines.

The schema allows to report on adverse reactions to any drugs (ADRs), adverse incidents on medical device, medicines that are not of acceptable quality and on fake medicines or devices. The incidents reported to Yellow Schema are then analyzed and tested to identify the new safety issues that may not have been identified earlier during clinical trial on the drug or vaccines in question. The report prepared are then studied by a group of medical experts which include doctors, scientist and pharmacists to find out the benefits and risks linked with drug. Necessary action is taken by MHRA if a new side effect is identified, after looking upon the side effects of other drugs used to treat the same disease. [39]. The UK Yellow Card ADR reporting form by both practitioners and patients are attached in AppendixB.

2.5.3 Centre for Adverse Reactions Monitoring(CARM)

The New Zealand Pharmacovigilance Centre supports the safety of medicines and related products in New Zealand through voluntary reporting of adverse events. CARM allows reporting of ADR by anyone who suspect an adverse event event. Healthcare professional reports are preferred as they will be able to add in more details about the medication use and the patient's history that are useful for evaluating the ADR. Anyone can report an suspected ADR but whenever possible they try to involve the patient's practitioners.It allows reporting through different means:- online forms, iOS application, freepost yellow cards, emails, fax and through telephone calls. They have the facility to record the message received through telephone outside office hours [40].

2.5.4 Vaccine Adverse Event Reporting System (VAERS)

The Vaccine Adverse Event Reporting System (VAERS) is vaccine safety surveillance program co-sponsored by the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA). VAERS is an adverse event reporting system that collects information about the adverse events happened due to a licensed vaccine in USA . Incidents can be submitted using an online form, or through FAX or can be submitted by an email. As per the data published in their site, there are 30,000 reports being reported to VAERS annually. 13% of the reports are associated with disability, hospitalization, life-threatening illness or death and are classified as serious. There are continuously monitored and it has helped to identify new rare but a serious consequences of vaccination [41].

2.6 Symptoms Description

Symptoms description is a prime part of adverse drug reaction reporting. The whole ADR phenomenon can be summarized under a symptom description perspective in the sense that an adverse drug reaction implies that a patient or individual is experiencing some adverse reactions (symptoms) after administering the drug in question. This goes to show how symptom descriptions can encapsulate the adverse drug reaction concept or at least form a core part of the phenomenon. Where there is an adverse reaction, there is a symptom that must be described in order for analysts to assess the drug's adverse effects. Therefore symptoms description is a critical area to look at under the drug adverse reaction reporting and pharmacovigilance in general.

It is a known fact that different patients expresses their symptoms and complaints verbally in different ways using multifarious terms. And an average patients cannot express the symptoms in a standardized medical terms that allows physicians go into the insight of the problem directly. When patients explains their symptoms to doctors, the doctors asks questions back to the patients to get a detailed description of the symptom, which helps them to diagnose the problem and give the necessary treatment to the patient. In the case of Adverse drug reporting by patients however, the patients write their symptoms which are often not complete enough. This makes it difficult for analyst/researcher working on the reports to do any useful analysis. The actual problem could be due to something else which might not be mentioned in the symptom description. Also, the individual's symptoms could be observed by the doctors which is not the case with the spontaneous reporting. Everything needs to be explained clearly. This reduces the efficacy of the reports.

When the patient tells the doctor, *"I have been coughing for the past 3 days"*, the doctors can ask questions to the patients like for example,

- Does it hurt while coughing?
- Do you bring up any phlegm when you cough? Is there blood?
- Is it worse during night?
- Do you take any other medication?

These conversations do not take place in the case where the patient describes the symptoms in the ADR reports. So reporters (the patients) need to write the description in such a way that it at least answers most of the essential possible follow up question needed for an effective analysis.

Charles Forsyth and K. Bonewit-West [12, 42] described the information necessary in order for a symptom description to be complete. The following information are needed for each of the symptoms that are described in the description,

1. **Location of the symptom:** The area of the body where the symptom is located. The location of the symptom should be described specific instead of mentioning it in general terms. For example instead of general terms like Head, Stomach etc, it should be more specific such as right side of the forehead, lower part of the abdomen etc.
2. **Quality of the symptom:** The quality of the symptom is the complete and concise description of the symptom. If the patient suffers from pain, then the character of the pain should be included in the description. The patient must describe the symptom fully as much as possible.
3. **Severity of the symptom:** This refers to the qualitative aspect of the symptom which includes,
   (a) Intensity of the symptom (For example, Mild, Moderate, Severe)
   (b) Number (For example, no: of nose bleeds, no: of convulsions etc. . .)
   (c) Volume (For example, volume of vomit etc)
   (d) Size (For example, size of the rash, size of the lumps etc)

4. **Chronology and timing of the symptom:** Chronology and timing of the symptom include the series of activities since the start of the symptom till the patient reaches the hospital for treatment. This includes details about the following,

   (a) **Date of onset:** The calendar date and time when the symptom occurred.

   (b) **Duration:** The duration of the symptom which is how long it lasts after it occurred.

   (c) **Frequency:** The frequency of the symptom refers to how often the symptom occurred since it started.

   (d) **Change over time:** This refers to any changes in the symptom since it first occurred.

5. **Manner of onset:** The manner of onset refers to what exactly the patient was doing when the symptom first occurred and what was experienced when the symptom began. For example, the patient may have been lifting a heavy object before he experiences lower back pain.

6. **Modifying factors:** Symptoms often are influenced by external or internal factors and activities such as exercise, change in weather etc., Ameliorating factors are those that makes it feel better and Aggravating factors are those that makes it feel worse. Some of the external factors are heat, cold, light, noise etc. Some of the internal factors are positions, activities, movements etc.

7. **Associated symptoms:** There is more than one symptom that are associated with a disease. The symptom description should also describe about any other symptoms that commonly occur with the main symptom described.

CHAPTER 3

Literature Study

This thesis work involved research into the ADR domain which included some literature reviews. Review of literature span from ADR reporting domain as a whole to specifically focusing on reporting with respect to symptom description. Our pre-thesis project we conducted earlier, focused solely on the literature review of ADR and helped us get an insight into the ADR, ADR reporting and its quality. In this chapter we present some of the selected literature that we reviewed with regard to their relevance to the thesis domain.

3.1 Review Methodology

The purpose of our literature review was to provide the current state-of-the-art of the ADR reporting process. This method helped us identify the recent research relevant to our research questions. The method follows the structured approach we employed in searching for articles, selecting the articles and finally reviewing a subset of them.

The literature reviewed were divided into two sets: The first set of literature were those selected during the our pre-thesis project. Those articles helped us get better insight into ADR reporting in general. We then further focused on symptom description and reviewed literature that addressed the different ways for symptom classification and the information that are necessary for the symptom to be more complete.

3.1.1 Search Phrase Construction

Here we constructed a number of keywords and primarily searched through four online publication repositories: JAMIA [43], Engineering Village [44], BJCP [45] and PubMed [46]. We first identified some relevant keyword from which we constructed some relevant key phrases. The following keywords and phrases and a combination of them were used; “Adverse Drug Reaction”,

"Adverse Drug Event", "Adverse Drug Event reporting", "Adverse Drug Reaction Reporting", "ADR Reporting", "ADE Reporting", "spontaneous reporting", "ADR", "ADE", "DDI", "Drug to drug interaction", "Pharmacovigilance", "Side effect reporting" and "incident reporting" . As much as possible we limited our use of Google Scholar since the result sets from Google Scholar were too large and diverse, filtering through such diverse information would prove challenging. We however included some articles from Google Scholar and Google search in general by doing random keyword searches and look-ups. In the second part of the search, we include some additional keywords like "symptoms description", "clinical symptoms", "symptoms classification" and "structured clinical text".

3.1.2 Selection Criteria

For each keyword search, we considered only the first 50 articles ranked according to relevance, publication date from Jan 1, 2005, or both, depending on which filtering parameters the publication website had available. While selecting the second set of articles, we included articles published till date. In the second level of screening, we cross referenced the article titles across the various results from repositories and took out duplicates. We further screened out more articles by manually reading the abstracts and discarding the less relevant contents. The articles were considered depending on whether contained information about some methods of improving the ADR reporting or detecting ADR reports. More articles were added to the primary list though snowballing; by going through the references of some of the articles we considered most relevant and including the articles they referred to. We used Zotero [47] in combination with Microsoft Excel to organize and manage the articles' references.

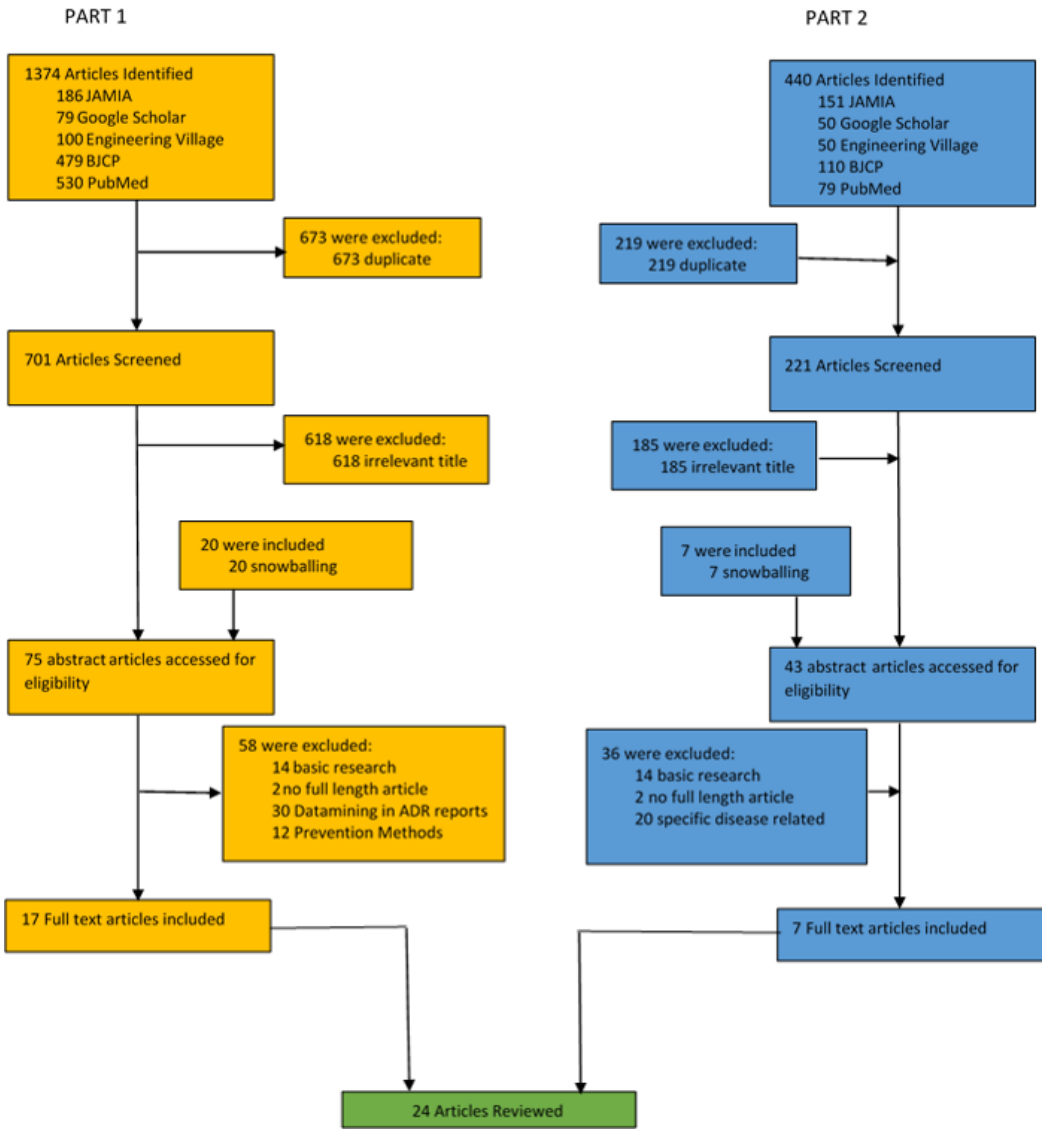

Figure 3.1: Flowchart showing literature research process

In the first part, a total of 1374 documents were retrieved from our query search, and from these we removed 673 duplicate articles. We then screened the articles and judged their relevance based on their titles. A total of 618 articles were removed using through document title screening. 20 articles were included as a result of snowballing. We finally read through the abstracts of the remaining 75 articles and decided on 17 of the most relevant documents. In the second set, a total of 440 documents were retrieved from our query search, and from these we removed 219 duplicate articles. We then screened the articles and judged their relevance based on their titles. A total of 185

articles were removed using through document title screening. 7 articles were included as a result of snowballing. We finally read through the abstracts of the remaining 43 articles and decided on 7 of the most relevant documents. Thus, a total of 24 articles were selected to be included in our review. The Figure 3.1 shows the results of the publication mining process.

3.2 State-of-the-art

In this section, we present the review of subset of the selected articles that are related to our project. By related, we mean that these articles address issues that are directly or indirectly related to adverse drug reactions and reporting. These articles either talks about some methods of improving the ADR reporting or some methods for detecting ADR reports. These sources served as the backbone that inspired our ideas for improving the domain and primarily formed part of our preliminary study while we acquired and developed our knowledge base on the ADR domain.

3.2.1 ADR Detection from EHR, Clinical texts and bio-medical texts

Many works on adverse drug reaction or event reporting, have been focused on retrospective data. The reason for the occurrence of adverse drug reactions can be attributed to many causes and include the occurrence of drug to drug interactions. Isabel,Paloma and Maria [11] in the article Extraction of Drug-Drug Interactions from Biomedical Texts, present the DDI-Extraction 2013 task which involved the recognition of drugs and extraction of drug to drug interactions that appear in biomedical text. A group of eight teams took on this challenge and developed systems to identify, extract and classify drug to drug interactions from an annotated corpus. The identification of drug to drug interactions is clearly a relevant issue.

In contrast to this method which deals with retrospective data, we propose and intervention into the biomedical text creation process that makes the extraction of DDIs simpler. Of course our proposed method is not a substitute for these text extraction techniques but should be seen as a complement since there is still a large body of clinical knowledge already in free text.Ideally we believe that instead of dealing with the problem in retrospect, pro active measures can be put in place instead.

Another method that deals with retrospective data proposed by Guan Wang, Kenneth et al. involves the discovery of adverse drug events in

clinical notes [48]. They argue that electronic medical records and free text of clinical notes provide the most complete and unbiased picture of clinical events available [49], as opposed to spontaneous reporting systems such as US Food and Drug Administration's FDA Adverse Event Reporting System (FEARS), the British Yellow Card System etc.They use millions of clinical notes along with prior knowledge of drug usages and known adverse drug events (ADEs) as inputs which are processed into statistics used by a discriminative classifier. The output of the system is the probability that a given drug-disorder pair represent a valid ADE association [48].

This is yet another retrospective approach that throws light on the potential gold mine of information that could be harnessed from free text medical records. This brings to mind the question; why not get the information at reporting time instead of going through the hustle of dealing with natural language processing concerns?

Ying Li et al. also describe another method of detecting adverse drug reactions using electronic health records. Here they focused on two serious adverse drug reactions, rhabdomyolysis and pancreatis; identifying them via established criteria , selecting potential confounders and then using penalized logistic regression to estimate confounder adjusted adverse drug reaction (ADR) associations [50].

3.2.2 Quality of the published ADR reports

In 2003, William N Kelly did a descriptive analysis on already published ADE case reports with an objective of finding completeness of the different variables that are reported in the ADE reports. The reports were selected such that their publication dates fell between mid-1970 to mid-1990. The study results showed that age, gender and recovery status were the three different patient variables which were reported in most of the reports, greater than 90% of the 1520 published ADE case reports. The only drug variable which was reported more than 90% is the ADE mechanism. The other 6 drug variables like dose, duration of therapy, indication etc were reported between 14 - 74 % of the time.

Most of the event variables were reported most of the time. In 61- 99% cases, were the added information for DDIs, medication errors and allergies reported. The drugs involved and the duration of the drug use in case DDI were normally reported. The route of administration was reported only for about 66%. Cases related to medication errors always reported what

actually happened but often missed how and why they occurred. There was place in the case reports for describing what took place, laboratory values of the patient and his progress but less attention were given to them [23].

In Oct 2012, Sánchez-Sánchez et al. in their study to evaluate the completeness of the information found that 32% and 40% of the ADR reports from 2007 and 2008 respectively were classified as group 0, which means that the information is insufficient to generate the risk signals. It is therefore important to focus the research on how to improve the completeness of the reports which improves the overall quality of the submitted ADR reports [51].

There are more recommendations available in the literature on how to improve the quality of the ADR reports after the initial evaluation by William N Kelly in 2003 on the quality of the published ADR reports. In the most recent study by the him in 2015, he analyzed the reports again with the aim of knowing whether the quality of the published reports had improved over the time after his evaluation. It is a two phase study with an additional objective to find whether quality of reports varies across journals. The phase-I study is exactly the same as the earlier study expect the case reports are published between 2000 and 2013. Phase-II used the same method as Phase-I with case reports selected from different journals over a period of 1 year. According to the conclusion, progress is made towards the quality of the report but still improvement is needed in order to make the data from the reports more understandable and relatable to patient care [52].

Singh and Bhatt evaluated the ADR reporting forms of 13 different countries and compared the similarities and dissimilarities among them. They found that there were only 13 common data elements which were captured by all the countries. The Malaysia and Canada ADR reporting forms captured the most number of data 43 elements and Brazil the least with just 17 elements. They then proposed a generic spontaneous ADR form with 58 data elements that are essential for effective assessment of the ADRs [53].

The above research throw light on the limitation ADR reports have had over the years as regards content completeness. Yet it is worthy of note that content in this sense and at a certain level of detail may not be patient oriented but professional-health-worker oriented. This must be kept in mind where ADR report content is under discussion and more especially where issues regarding completeness arise.

3.2.3 Improving ADR Reporting

Virginia L. Hinrichsen et al implemented an automated vaccine adverse event surveillance and reporting system situated in an electronic medical record in order to improve under-reporting and incomplete reporting that is prevalent in spontaneous reporting systems. Potential Vaccine adverse events were flagged and alarmed to prompt clinicians to attend to the possible adverse event [54] Clinician surveys indicated that it took less amount of time to attend to the alerts and it can be argued that this indicates the value time plays in reporting. Reducing the amount of time spent on reporting is a good motivator for adverse drug event reporting.

Over a two year period, AJ Avery et al. conducted a case study to evaluate patient reporting of adverse events and assess the drug monitoring impact of patient reporting through analyzing the reports of suspected ADRs through the YCS [39, 55]. The study revealed that patients reported more cases than health care practitioners and had a higher number of suspected ADRs. Reports by patients were richer in detail and better described the impact of side effects.

Adverse events are directly affect patients and therefore it is only natural that patients have an opinion in the matter. The contribution of patients cannot be overlooked so its not far fetched to ask for research into improving the reporting process by patients.

3.2.4 Symptoms Classification

When patients express their bodily symptoms to the doctors, the doctors seek to understand them by making diagnosis. When a diagnosis is made in terms of bodily pathology, they are regarded as "medically explained". If not, a psychiatric diagnosis is made and they are regarded as "medically unexplained". Thus symptoms are classified as either bodily pathology or psychopathology. These are based on the assumptions that disease pathology explains bodily symptoms, those that are not explained by it are explained by psychopathology, and it is also clinically useful to classify unexplained bodily symptoms as psychiatric and explained symptoms as medical.

Sharpe et al. examined all these assumptions and suggested better alternatives. He proposed three requirements for such diagnostic systems. The first requirement is that instead of categorizing the symptoms, the symptoms should be treated on its own. The second

requirement is that multiple etiological factors like social, physiological and biological factors should be considered and not just the bodily pathology or psychopathology. The last requirement is that it should encourage a more integrated approach but not avoid the traditional dichotomization of patients into medical and psychiatric categories [56].

NCHS (National Center for Health Statistics) developed a methodology for symptom classification for their sole use. Their symptoms classification has two divisions:- the tabular list and the alphabetical index of the terms. The tabular list consists of 13 classes that are again divided into individual categories or rubrics. The NAMCS coding schema consists of 197 rubrics grouped into 13 classes [57]. These classifications has the grouping of the similar symptoms under one class which helps in processing and presentation of statistical data.

Charles Forsyth classified symptoms as either sensation, feelings, bodily functions, activities or behaviors. Some of the examples for a sensations are pain, numbness, itching etc. Examples for feelings include sadness, anxiety etc. Examples for bodily functions include urination, sleeping, passing gas etc. Activities and behaviors examples are restlessness, twitching etc [12]. We used this classification in our experiment for evaluating the completeness of the symptom description.

The research area that has to do with symptom classification is rather important to our work because the aspects of improvements we looked into in this work had to do with grouping symptoms in classes to promote easier analysis. It is easier to deal with symptoms as a group than individually.

3.2.5 The relevance of ADR Reporting

The death of Hannah Greener on the 29th of January 1848 after she was given chloroform before treatment for an ingrown toenail followed by the Thalidomide tragedy in 1961 that rendered many new born babies physically defective are good enough reasons to see the relevance of ADR reporting. Cases as such only came to light after vigilant observations were made. The habit of reporting adverse events is a vigilant exercise and cannot be overlooked [32–34].

Judith K. Jones shared an incident that happened when she was the in-charge of the post-marketing of drug safety program at the US Food and Drug Administration (FDA) in the early 1980s. A physician who was working in the neonatal intensive care unit informed informed him through

a phone call that he thought that they were killing babies. When the physician calculated the daily dose of the benzyl alcohol, an antibacterial preservative found in the flushing solution for arterial lines, he found that the proportion of daily dose to the neonatal weight exceeding the toxic levels. The physician was worried that this might be doing more harm than good and cited many deaths that might have been related to this. Judith K. Jones asked the physician to submit the report to the FDA. The FDA examined the case and finally withdrew them from the market. This phenomenon clearly advocates the importance of ADR reporting and proves how the alertness of the healthcare provider made a difference [8].

One could wonder where symptoms description comes in all this talk about pharmacovigilance and ADR reporting. Symptom description is an integral and imperative part of ADR reporting and where it is not, it should. Both terms adverse events and adverse reaction imply some sort of phenomenon that the a reporter is going through or has gone though. If a drug has caused an adverse event then there may be signs that indicate this event or reaction hence symptom description. According to a survey on the the National Ambulatory Medical Care done by Meads and Mclemore [58] we find that physicians are asked to record the symptoms of the patient 'in the patient's own words'. This says a lot about the relevance of records taken from the patients' perspective given that a physician's observation alone may not suffice. K.L White advocates the importance of symptom data as a valid measurement in planning medical care. He states that:

> *Medical care services have to be planned on the basis of the prevalence of symptoms and complaints, not discharge diagnoses or deaths. Symptoms and complaints are the input of the health services system; discharge diagnosis or deaths are the outputs*

So long as record keeping 'in the patient's own words' is concerned, there are consequences that cannot be overlooked. It is generally known that patients hardly specify a disease entity when they seek medical care. You would hardly find a patient using terms like duodenal ulcer, bronchopneumonia and psychoneurosis, but rather terms like vomiting, pain, cough and sleeplessness are more common. White [59] stresses the need to pay attention to symptoms as opposed to being in haste to make a diagnosis since a diagnosis is merely an intermediate step in the process of resolving the patient's complaint. His

argument calls for a closer look at symptoms descriptions, especially from patient's perspective.

3.2.6 A look at ADR Reporting

In the course of our literature study we identified that most countries do now allow adverse drug event reporting by both healthcare professionals and patients or anyone who wants to report an adverse event, however the content of reports and the number of people subscribing to these reporting schemes varied. With the exception of countries like india, most of the schemes support both paper-based and online forms

Content

There is currently not a single standard reporting format recognized internationally for submission of adverse drug reaction information to national health administration agencies. Council for International Organizations of Medical Sciences (CIOMS) reporting form is an internationally recognized reporting format, which was designed in 1990 for reporting the ADR case information to regulatory bodies. This form was developed for providing ADR information on the new molecules which are under clinical trial by Marketing Authorization Holders (MAH) to regulatory body, but it does not solicit case information from health professionals or even patients.

A study in 2012 by Singh and Bhatt [53] showed that data such as age, height, body weight body mass index (BMI), and body surface area (BSA) which are important parameter for evaluating an ADR were not all available in adverse drug reaction forms used by many the countries they considered. BMI and BSA determine the correct dosage for a particular individual, especially for drugs with low therapeutic index. Patient's weight and height determine BMI and BSA hence making mention of them in the report is important.

Ethnicity is another parameter worth considering since it highlights the diversity of different ethnic groups to associated risk factors. Ethnicity and maternity status are included in forms for health care professionals but that data is not captured in patient forms. While UK's Yellow Card Scheme and India's ADR reporting scheme provide a free text field for the entry of relevant information like whether the patient has allergies, smokes, drinks etc, the Center of Adverse Reactions Monitoring in New Zealand specifically captures such data in separate field. Drug name, dosage, route of administration, frequency, start date and stop date are parameter necessary for the determina-

tion of whether the cause of the reaction is as a result of the drug or incorrect dosage. Neither UK, New Zealand nor India include route of administration.

According to Singh and Bhatt [53] the national Adverse Drug Reaction reporting schemes in Malaysia and Canada recorded the most number of relevant parameters in their ADR forms.

Participation

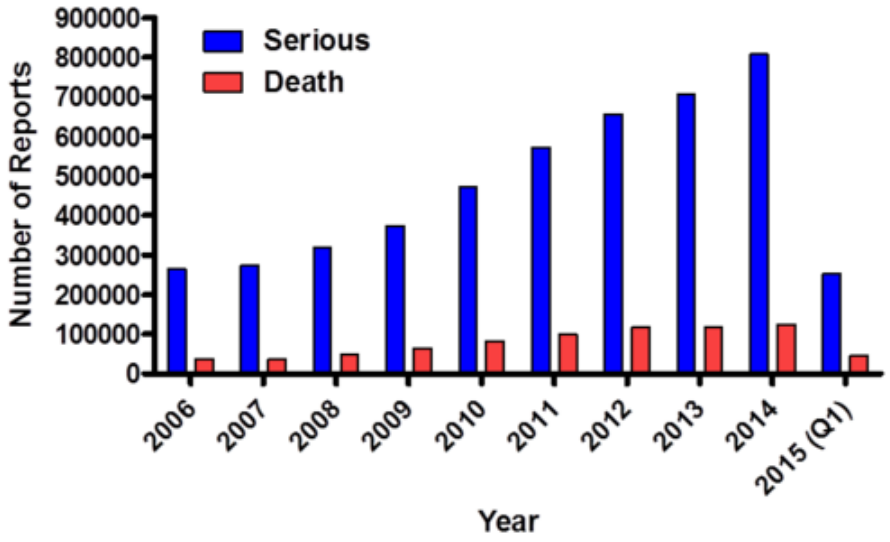

Figure 3.2: Patient outcome(s) for reports in FAERS since the year 2006 until the first quarter of 2015. Serious outcomes include death, hospitalization, life-threatening, disability, congenital anomaly and/or other serious outcome [10]

There is still under-reporting as most of the countries follows voluntary or spontaneous ADR reporting. In the Indian ADR reporting scheme, only healthcare professionals are allowed to report adverse drug events. [53]. Though there is under-reporting, the statistics shows that there is steady increase in the rate of reporting. The UK Yellow Card Scheme recorded 3.6 percent increase from 2011 to 2012 and 4.1 percent increase from 2008-2012. The number of general practitioners that report to the scheme increased by 26 percent since 2007 while pharmacist participation increased by 19 percent and nurses increased by 17 percent . [60]. US FAERS recorded a steady in-

crease in the number of recorded reports over the period of 2006 to 2015 [10]. Figure3.2 shows a graph of the recorded number of reports over the years

Mode of Reporting

Many of the adverse drug event reporting schemes provide for patients and health professionals both paper-based and online forms for reporting and the UK Yellow Card Scheme and FAERS are examples as such. In India the mode of reporting adverse drug events is only paper based. The form must be filled and sent to the nearest Adverse Drug Reaction Monitoring Center by health care officials. The electronic version of the forms are however currently under development [61]. None of the current forms however though electronic are interactive.

US's FAERS and New Zealand's CARM also accept reports through phone calls. Individuals who suspect adverse drug reactions can call the agencies in charge and report as such. The calls are recorded and processed at a later date.

Time

Another factor that influences quality of reporting is the time taken to fill-in the reports. There are personal patient information that do not change or at least do not change frequently. Such information can be automatically retrieved from electronic health records to partly fill spontaneous adverse drug event reports. This is sort of a dependent quality factor such that there should be such patient information present in electronic health record as well as standard data exchange and transfer formats that are already available.

CHAPTER 4

Methods & Approach

In this chapter we present and explain the method and the approach we adopted in executing this work. The methodology we adopted in this project took three forms; thus a research method into the quality of of ADR reporting that led to a subsequent design of a quality model and an evaluation of symptom descriptions with respect to the model and an implementation of a supporting prototype for our work.

Here we realize a quality assessment model that we use to evaluate sample symptom descriptions collected through a survey. We further assess the quantitative value of symptom descriptions.

In our approach we:

- Research into ADR reporting Domain
  - State of the Art ADR reporting
  - Quality of ADR Reporting and Reports
  - Build a knowledge base from the research
- Design Quality Assessment model
  - Design AC3 Model: Adequacy,Completeness,Correctness & Consistency Model
- Conduct Symptom Description Survey
  - Conduct experiment through a survey
  - Collect sample symptom descriptions via the survey
- Conduct Symptom Description Completeness Assessment Survey
  - Conduct experiment through a survey

  - Design the survey for quantitatively grading the completeness of symptom descriptions

- Study, analyze and expand symptom descriptions to support case
  - We study the symptom description collected from the survey and identify common language patterns.
- Evaluate the quality of the symptom descriptions
  - We evaluate the descriptions collected from the survey both qualitatively and quantitatively.
- Propose and develop a prototype with informed from the our evaluation.
- Plan a user acceptance test process for the prototype
  - Conduct test to compare prototype with a free text field
  - Conduct test to assess user acceptance of the system
- Describe the features of the advanced system

4.1 AC3 Quality Assessment Model

In our research to tackle the issue of what 'improvement' means, we look at ADR reporting through the following quality measures or indicators; Completeness, Consistency, Accuracy and Adequacy. The choice of these quality measures was inspired by the work of Didar Zowgh et al; The Three Cs of Requirements [56], where they tackle issues on the Correctness, Consistency and Completeness of requirement specifications.

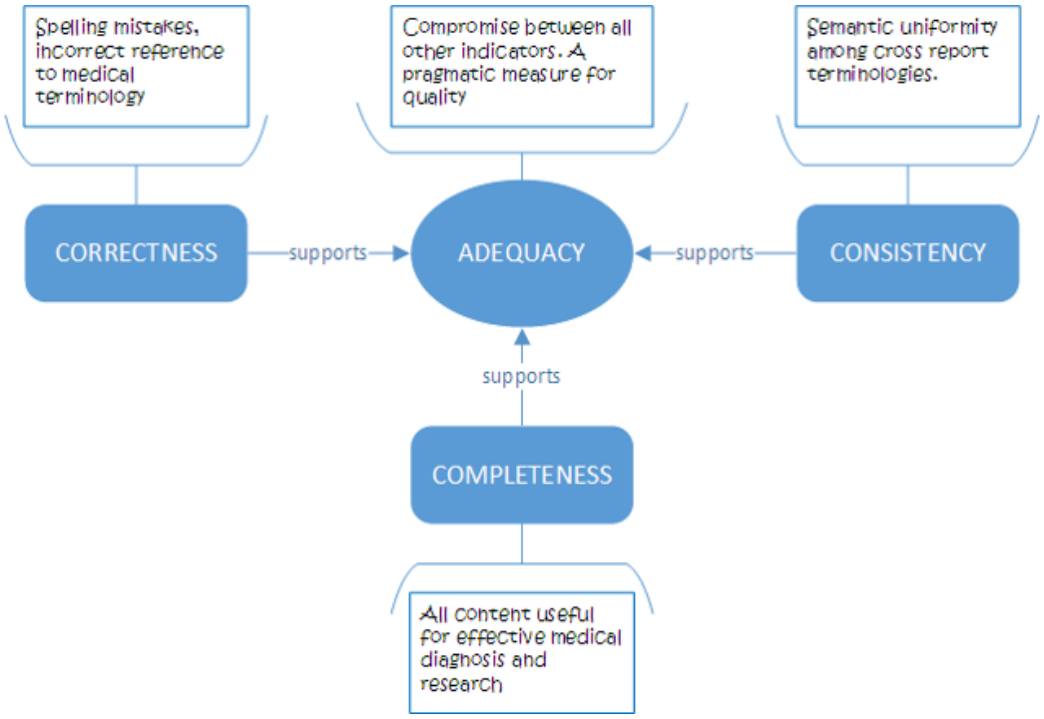

Figure 4.1: The AC3 Quality Model

4.1.1 Completeness

The quality of ADR reports has a bearing on how much information or data is actually available for consideration. Where ADR forms are concerned, some information may be omitted or overlooked by reporters and we seek to review and discuss the implications of this phenomenon.

The concept of *Completeness* is always with respect to a predefined measure and therefore cannot exist as an isolated term. We need to define some indicators that are required in order to term a description as complete otherwise doing so is without validation. Without these indicators, there is hardly a way to define a description as complete since the concept of completeness is porous without a reference to a predefined measure. When we have these comparative or reference measures in place then we can measure the completeness of a description based on that specific criteria.

The symptom description must accurately describe in detail the various characteristics of symptoms. It should answer the following questions about the symptom [12]:

- Location - where is it?
- Size - what area is involved?
- Does it extend or radiate anywhere?
- Does it move or spread with time?

4.1.2 Consistency

To assist the process of information extraction and analysis a level of consistency regarding data collected from ADR reports is of importance. This implies that, it is an advantage that concepts and vocabulary as well as their semantic meaning be uniform across collected data.

Consistency is a tricky quality to measure owing to the fact that in order to achieve consistency across symptom descriptions, there must be a defined reference for the terms in the description. Say for instance three different patients state in their description that they experienced, common cold, flu and influenza respectively. These three terms primarily refer to the same thing or at least are somewhat similar and therefore have a semantic relationship. The identification and establishment of such a relationship or link is how we measure consistency in this model. With consistency we can verify that two terms primarily refer to the same semantic concept,value or entity. Also the content of the description as regards the subject being described must be coherent.

4.1.3 Correctness & Accuracy

Data that is collected via reports should be accurate and verifiable. For instance the Age and Gender of the patient reporting the ADR or the patient for which the ADR is being reported should be accurate. Also issues of spelling and short-hand texts cannot be overlooked especially in cases where ADR/ADE forms have free-text sections which means that reporters are free to type anything they please into the fields. The terms 'doctor' and 'dr' do not necessarily mean the same thing even though may be used interchangeably where free text fields are used to collect data.

Looking at this from another perspective we find that 'Correctness' is almost impossible to validate since it is a subjective measure and relies on the reporter's integrity. Whether a patient accurately describe what

they feel or whether their description is even true is almost impossible to tell. Exercises like this depend on the integrity of the reporters to tell the truth or at least express their symptoms most accurately. To a large extent, expressiveness is dependent on the reporters scope of knowledge and understanding of the language being used and so verifying correctness in this respect is cumbersome. Therefore, in our work on symptom description we consider correctness in terms of the common human errors made when writing medical terminology and describing symptoms.

4.1.4 Adequacy

This is a holistic measure that tells whether the supposedly correct, consistent and complete symptom description is useful for any further medical diagnosis or research. The relationship between completeness and adequacy is such that unlike completeness, adequacy is a more pragmatic and realistic measure. Completeness seeks to answer the question " Does the report contain all these required criteria for describing symptoms?". Adequacy on the other hand seeks to answer the question, "Using whatever information available, whether complete or not, can relevant medical diagnosis be made from such information?" This open ended nature of the Adequacy Measure, makes it difficult to ascertain. How adequate is adequate?

While we discuss the above areas that we believe contribute to the quality of ADR reports and hence are in line with the topic of 'Improving ADR reporting' we specialize on a specific aspect of the domain which has to do with the introduction of a controlled language concept into ADR reporting process. Controlled language here will incorporate controlled vocabulary as well as controlled English for all Free-Text supported field for ADR reports especially that for Symptom Descriptions. Suggestion of medical terminology will fall under controlled vocabulary. We seek to narrow down our study to the incorporation of controlled language into symptom description.

4.2 Symptom Description Survey

A survey was conducted to retrieve sample symptom description from potential patients and its purpose was to collect information on how typical patients describe their symptoms. This was an online survey created with *Google Forms*. In the survey, individuals were asked to describe, come up with or remember a case where they had experienced symptoms from taking a drug and then describe the symptoms as they would in an ADR report.

In this experiment, we sent out form to a group of 143 participants and out of that lot 25 of the participants responded with full body text descriptions of symptoms they had experienced from various drugs. We collected symptoms descriptions in the English language only.

The survey required participants to describe, through text, any adverse effect or reactions they have experienced in relation to taking a drug. The electronic form was sent out via email.

4.2.1 Goal

The goal of the survey was to collect real symptom descriptions from individuals and analyze toward the validation of some hypothesis. The survey was to help evaluate the language structure and terms used by patients in describing their symptoms and subsequently help develop a cut-through template.

4.2.2 Hypothesis

Patients adopt similar language structure, expressive terms and patterns when describing their symptoms.

4.2.3 Design

The survey was designed as an online questionnaire where we asked for the age, gender and nationality of the participants in addition to their symptom descriptions. This information was to give us insight into the language used by non-native English speakers as well as native speakers especially because the set of target participants were of multinational. We conducted the survey in Trondheim, Norway, where the people are diverse in nationality and culture.

4.2.4 Recruitment of Participants

Though the ideal target group for the survey would have been hospitalized patients or patients who have actually had drug adverse reactions, we supposed that many individuals throughout their lifetime may have most likely experienced a drug adverse reaction of some sort. Therefore our friends,colleges and acquaintances were the target group we used for this survey.

4.2.5 Analysis

We adopted a manual approach in analyzing the responses received from the survey and the analysis was mostly of a theoretical nature. In this analysis we looked out for a number of indications that could affect the quality of the symptom description, and these include:

- Reference to drug names and drug groups
- The level of detail to which the symptoms were described
- The length and breadth (scope) of the description
- The coherence of the language used
- Grammatical accuracy and spelling
- The sophistication in the language used

4.3 Quality Assessment Survey on Symptom Description Completeness

This survey was conducted to collect the opinion of health specialists, on the importance of certain basic information needed in symptom descriptions, to a number of symptoms. These basic information as described by Charles Forsyth and K. Bonewit-West [12, 62], are relevant for the effective evaluation of symptoms. We use Forsyth and K. Bonewit-West's research as a benchmark to characterize the completeness of symptom descriptions.

Typically, symptoms given by patient should be expected to contain certain basic information like the symptom characteristics or type (feelings, sensation, bodily function etc.), We refer to these characteristics as the categories of symptoms. The real measure of the quality of this description then falls on whether these characteristics are described well or even described at all. According to K. Bonewit-West, there are seven basic information needed in order to effectively analyze a symptom description [26]. These include:

1. Quality of the symptom,
2. Location of the symptom,
3. Severity of the symptom,
4. Chronology and timing of the symptom,

5. Manner of onset,
6. Modifying factors,
7. Associated symptoms.

We add another factor 'Suspected Cause' which can double as a description-wide factor. This means that the patient may mention a general suspected cause for all the symptoms they experience or give suspected causes for each depending on the context. In this context in particular, the suspected cause will be the drug in question.

The factors above can be encapsulated under Quality/Characteristics of symptoms in the sense that any symptom that is named is very likely to be be a feeling, sensation, bodily function or behavior and for every characteristic, factors such as location, intensity, frequency, time of inception etc. apply.

Of course it makes sense to say that for a stated symptom, the presence or absence of its associated symptom in a description should not necessarily carry the same weight as the location or severity of the main symptom but then again what does a main symptom even mean. To make this clearer and eliminate any controversy, the main symptom in a description will refer to the symptom currently being described.

From this point of view, we attempt to ascertain our claim by conducting another survey. We undertook an experiment to formulate a grading scale to evaluate the completeness of symptom descriptions.

For each named characteristic in the description we expect to have accompanying information like, location, time, frequency etc. And each of these information should have a weight depending on their relevance to the symptom in question. While weighting can be done under the assumption that the relevance of factors and sub factors are uniformly distributed and hence can have uniform weights, this is not pragmatic. It makes sense to say that for a symptom such as headache or stomach pain, information about the location of the symptom is redundant since it is inferred in the name of the symptom. The information however, though redundant, may not necessarily be absolutely irrelevant.

We therefore use the above argument to formulate the hypothesis that,*when grading a given symptom, the set of basic information required and considered for grading should not have equal weights and that symptoms that belong*

to the same category (feeling, sensation, bodily function or behavior) can have similar weights. We go ahead to test this hypothesis through a simple experiment.

4.3.1 Hypothesis

H1: The type and degree of relevance of basic information needed in the description a symptom vary depending on the kind of symptom or the category the symptom belongs to. It is necessary to note that the relevance of factors in this case are with respect to each other.

H2: Symptoms that belong to the same category can have similar weight grades.

4.3.2 Goal

The goal of the survey was to develop a quantitative grading scale for the completeness of symptom descriptions. This would help to quantitatively compare the completeness of different symptom description texts.

4.3.3 Design

The survey was designed both an electronic and paper based form and was optimized to reduce fill-in time. Due to how busy the target groups for the survey were, it was necessary to design the survey as simple as possible. We designed the survey to last between 5-10 minutes and though this constraint no doubt affected the detail of the survey questions, we believe that the responses received were still relevant. We had to adopt an unconventional layout in the empirical design of the questionnaire in order to not discourage participation. Adopting the conventional Q&A layout would have made the questionnaire too long.

FACTORS / SYMPTOMS	Quality of Symptom Complete and concise description of the symptom			Location of symptom Area of the body symptom is located			Severity of symptom Symptom intensity			Chronology, Frequency &Timing Symptom frequency and timing		
	Degree of Relevance To Symptom											
	Low	Med	High	Low	Med	High	Low	Med	High	Low	Med	High
Headache	○	○	○	○	○	○	○	○	○	○	○	○

Figure 4.2: Two Dimensional Questionnaire with three-scale rating

The survey took the form of a two dimensional tabular structure where the rows were the symptoms (dizziness, itching etc.) and the columns were the factors. Participants were to grade each symptom according to a three-scale rating representing low, medium and high levels of relevance respectively. See Figure4.2

Two to three symptoms were selected from each of the four symptom categories, thus sensation, feeling, behavior and bodily function.

Table 4.1: Symptoms selected from each category

Symptom Category	**Symptom Example**
Sensation	Headache
	Itching
	Nausea
Feeling	Sadness
	Dizziness
Bodily Function	Swelling
	Coughing
Activities & Behavior	Twitching
	Restlessness

4.3.4 Recruitment of Participants

The target participants for this exercise were general medical practitioners, nurses and pharmacists. However among the group of participants, pharmacist were the ones most willing to participate in the exercise.

4.3.5 Analysis

The data was analyzed with respect to the earlier hypothesis. Medical professionals like general practitioners, nurses and pharmacists usually have opinions on symptoms and drug related issues based on their experiences. In our analysis, we watched out for the opinion of these health professionals in support of our hypothesis. The analysis focused on extracting a relative grading scheme from the opinions submitted by participants. Our analysis included observing.

- The mean grades for factors with respect to symptoms.

- The similarity between grading for symptoms from similar categories.

4.4 A Controlled Language Perspective

Controlled natural languages (CNLs) are subsets of natural languages that are obtained by restricting the grammar and vocabulary in order to reduce or eliminate ambiguity and complexity. The need for controlled natural languages arise due to the inherent ambiguities that come with all natural languages. In order to formalize a language, thus make it easy for humans to read and understand or make it machine readable, there is a need to eliminate these ambiguities. This brings about the necessity for controlled language.

Controlled languages based on natural language fragments, usually target technical domains and are designed to be unambiguous. The main reason for using a natural language fragment rather than a formalism is to have a notation that is readable without special training [24]. Controlled natural language usually falls between two categories; controlled language that focuses on human readability and ambiguity elimination and the other which focuses on controlled language that enables reliable automatic semantic analysis thus machine readability . The former is usually used in industry to increase the quality of technical documentation. The later however have a formal syntax and semantics and hence can be mapped to a formal language such as first order logic [63].

The advantage of controlled vocabulary is that only terms that are identifiable and familiar are allowed and this makes post processing easier. There is an advantage of having medical terms uniform across documents or reports and controlled vocabulary is a way of achieving this. It is necessary to note that this is what we mean by cross-report consistency.

4.4.1 SNOMED CT

SNOMED CT supports the development of comprehensive high-quality clinical content in health records. It provides a standardized way to represent clinical phrases captured by the clinician and enables automatic interpretation of these. SNOMED CT is a clinically validated, semantically rich, controlled vocabulary that facilitates evolutionary growth in expressivity to meet emerging requirements [64] SNOMED CT has a rich database of medical terminology that can be used in the ADR reporting domain. The advantage here is the means to normalize medical terminology across reports and promote the analysis of reports semantically.

Medical practitioners and professionals are well aware of medical terminology and hence can directly attest to the usefulness of SNOMED CT. The idea here is to get patients who report their symptoms to use uniform and semantically recognizable terms. This is hard since lay people may not be knowledgeable enough about the domain to do so. This is where our suggestion of having guided reporting through suggestion and auto-completion of medical terms comes in. This approach gives the informs the reporter of terminologies that are consistent with SNOMED CT and suggest the appropriate terminologies at reporting time.

SNOMED is based on "concepts." Each concept represents a unit of thought or meaning and is labeled with a unique identifier (computer readable). The phrases in human language used to describe the concept are called "descriptions" (or synonyms). Each concept has one or more descriptions linked to it. Each concept is interrelated to other SNOMED concepts that have logical connections to it. Relationships are used to provide a computer readable definition of the concepts. These definitions greatly enhance the value of the data collected, allowing it to be searched, retrieved, reused or analyzed in a variety of ways [64].

The truth is that people often have different ways of saying the same thing. By linking synonymous terms to a single concept, SNOMED CT allows computer systems to recognize the common meaning of synonymous terms. Thus, reporters can use various synonyms as they are accustomed to doing, but these synonyms will map on to the same concept.

Of course there is a need to consider the naivety of reporters. While health professionals may be privity to the technical terms that are available in SNOMED, lay reporters are not and therefore the simplest alternative descriptions form concepts is what should be made available to reporters.

Medical reports are usually collected in free text and the medical terminology content later encoded. We propose a way to involve the patient in this encoding process by providing an interface that interacts with the patients by providing suggestions for terms during reporting. Having clinical information stored in ways that allow meaning-based retrieval increases the benefits of stored information, The added benefits range from increased opportunities for real time decision support to more accurate retrospective reporting for research and management.The objective here is to facilitate the accurate recording and sharing of clinical and re-

lated health information and the semantic interoperability of health records.

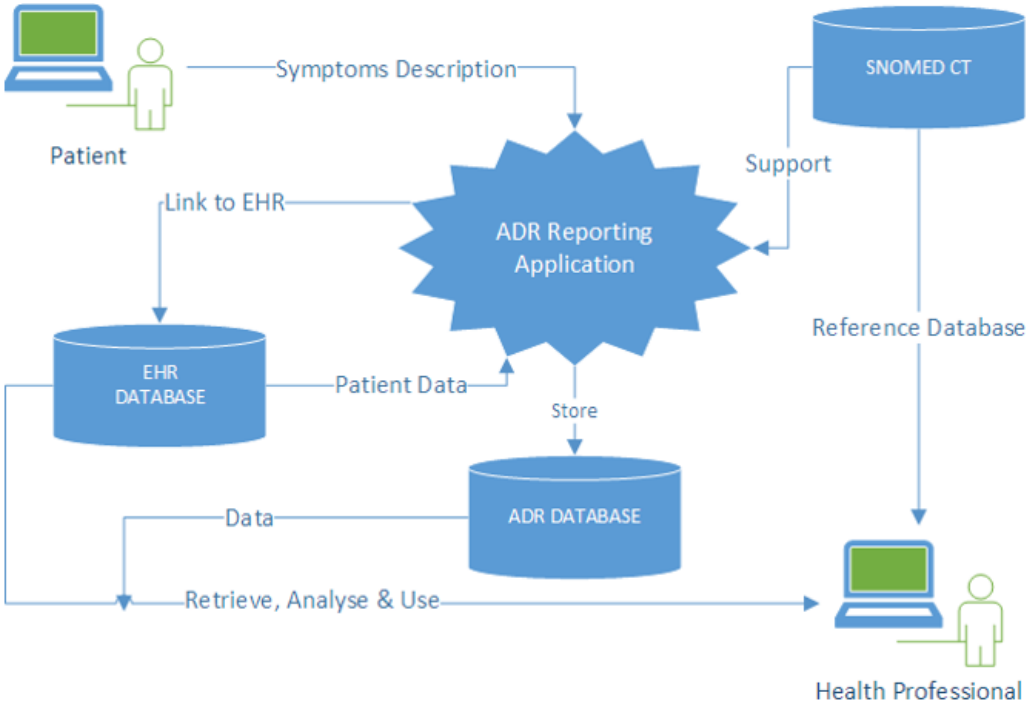

Figure 4.3: The Proposed ADR System Architecture

Figure4.3 above shows the our proposed schematic architecture of how ADR reporting can be linked to SNOMED and how patients and professionals contribute. ADR reporting is vital for medical diagnosis and therefore perhaps the reporting medium should not only be a form but a full featured application that can addresses quality through our proposed AC3 model.

Machine readable data refers to data that can be read and understood by computer systems with no or limited human intervention. It is interesting to see how this applies to the ADR reporting domain and specifically to Symptoms Description. Patients usually describe their symptoms in free text; and this is useful in the sense that it guarantees that reporters have the freedom to express what they feel without any linguistic constraints. While this approach is a plus in terms of patient freedom of expressiveness, it creates challenges where machine readability is considered. Such data are not automatically readable by machines because they have no specific format. Natural Language Processing research has its fair share of challenges in this respect and there is a lot of ongoing research to improve the issue.

However, even expressiveness has its limitations where patients are concerned. The level of an individual's expressiveness can be said to be a function of how much knowledge and understand they have of the language they are using. The subjective nature of expressiveness in this respect is in itself a challenge. The bottom line is that while expressiveness is necessary for symptom description, there are still some known and identifiable information that make a symptoms description most useful for further medical diagnosis and research. Expressiveness is not very useful if it lacks the vital information needed. Dr. Charles Forsyth in his write-up [12] identifies some key information that is needed when a patient is describing symptoms. Medical work is like detective work, and a significant part of the diagnosis (understanding what is going on and why) and the subsequent selection of appropriate management, is based on the accurate information the patients give. The symptoms and their details are the clues - and without decent clues it can be very difficult to undertake any relevant diagnosis. There are some key factors a symptom description must respond to:

- Detailed description of symptom characteristics
  - Sensation
  - Feelings
  - Bodily Functions
  - Behavior
- When the symptoms begun
- Details on Causative Factors
- How the Symptoms change over time
- What factors make it worse or better?

In the case of ADR reporting the primary causative factor will be the drug or drugs in question, though there may be other secondary or associated causes.

4.4.2 The Norwegian Prescription Database

The Norwegian institute of public health provides a database of all dispensed drugs in the region. It contains information about the users of a particular drug or drug category and the data can be split by sex, age and even geography. [42] Such a resource is especially suitable for our proposed method

for ADR reporting. Drug names, groups can be extracted from this resource to augment ADR forms. This is one step toward consistency across reports. The resource provides information on prescribed drugs which gives an added advantage. It is more suitable to refer to the drugs that have been prescribed frequently and within a specific time than the whole database of drugs. Execution of queries are less expensive and extraction time for the data is shorter this way.

4.5 Symptom Description from the AC3 Model Perspective

Looking at symptoms descriptions in terms of the AC3 Model, we went through the sample descriptions collected from the survey and established a metric for measuring the quality indicators. Quality indicators such as completeness, consistency, correctness and adequacy need to be measurable. While qualitative measures serve their purpose, we open the scope to look at the AC3 model from a quantitative perspective also. So how do we formulate a quantitative representation for the indicators?

4.5.1 Completeness

As we mentioned earlier, there are basic information that are required by health professionals to make relevant diagnosis. A symptom description can be said to be complete if and only if it satisfies all these set of requirement. Complete is an expandable concept in the sense that it incorporates the width (scope) and depth (detail) of the domain under discussion. Therefore there is a need to establish boundaries when we address the concept of completeness. The issue of completeness is particularly relevant because when it comes to symptom descriptions, the level of detail physicians look out for are usually high; there are many questions, follow up questions and examination that may take place when analyzing symptoms. However, asking this level of detail in a ADR form may tend to be cumbersome for the patients and perhaps negatively affect reporters' willingness to contribute to pharmacovigilance by submitting ADR reports. So there must be a level of detail of symptom descriptions that is acceptable to physicians and that patients or reporters can tolerate.

With respect to completeness, we limit our scope to a merger between the factors proposed by Charles Forsyth and K. Bonewit-West in their respective write-ups on the basic information needed in symptom descriptions that facilitate effective analysis [12,26]. We propose a simple measure for completeness as the ratio between the number of factors that make up a complete descrip-

tion and number of factors actually addressed in the description in question.

$$Completeness = \frac{\#\ of\ factors\ addressed}{\#\ of\ factors\ required} \tag{4.1}$$

4.5.2 Correctness

Perhaps the most important aspect of correctness is that which has to do with reporters' integrity. What is the point of analyzing ADR reactions reports that are not authentic? This aspect however, is challenge to measure, so here we focus on the less cumbersome and perhaps more realistic aspect; the accuracy of terms and vocabulary in description text. One might think that the issue of accurate drug naming and spelling of symptom terms is a trivial task; but this is not necessarily the case. For search based natural language processing techniques, the accurate textual representation of terms are not irrelevant. Correctness can be defined as the degree to which the symptoms description are free of errors. We characterize correctness as the ratio of the number of unidentifiable terms to the total number of terms in a symptom description text

1. Is there any misspelling in the medical terms?
2. Are the drug names or drug groups correctly referred to?

$$Correctness = \frac{\#\ of\ unidentifiable\ items}{\#\ of\ total\ terms} \tag{4.2}$$

4.6 Consistency

We look at consistency within reports as well as from a cross-reporting context. Similar medical terms, drug names and groups referred to in reports should be the same or at least have the same underlying semantic value. It should be possible to make reference to terms and terms for identifying drug or drug groups should be uniform across reports. The prescription database provided by The Norwegian Institute of Public Health is a step in the right direction toward our consistency goal. This resource can be used to achieve consistency across drug names and groups. A resource as such reduces the weight of data extracted in that when dealing with reports in Norway, there is no need to consider drugs or drug labels in India. It also makes more sense to extract drugs names from the set of the most frequently and recently prescribed drugs than from the database of drugs available in a

location. The execution and extraction time for data is less this way. Two reports are consistent if the same terms are used to refer to the same concepts.

For a number of considered terms or concepts 'n', we calculate consistency as the average of the sum of the inverse of the total number of terms 'N' that refer to the same concept. The value of consistency in a description is between 0 and 1 where the higher the value the higher the consistency.

$$Correctness = \frac{1}{n} \sum_{i}^{n} \frac{1}{N_i + 1} \tag{4.3}$$

Where,
n : Total number of terms,
N_i : Total number of terms similar to term i.

4.6.1 Adequacy

As explained earlier, adequacy is the term we use to refer to the more pragmatic form of completeness, correctness and consistency. In this measure, error tolerance is taken into consideration.

CHAPTER 5

Implementation

In this chapter we introduce our implementation of a web based prototype that supports our proposed quality model for ADR quality improvement. The focus of this implementation was not to realize a full-featured application but to demonstrate how the aspects of quality, thus consistency, correctness and completeness can be realized and tested.

5.1 Symptoms Description Template

The reason for conducting a survey to collect sample symptom descriptions was to come up with a proposed template that would hopefully cut across multiple expressive divides. We attempt to make the process of expressing symptoms easier and hopefully provide a level of interactivity that will improve ADR reporting participation.

The description template was to be used in place of free text fields in order to achieve a higher level of control over what data is collected from reporters. Figure 5.1 shows the template we developed from our research.

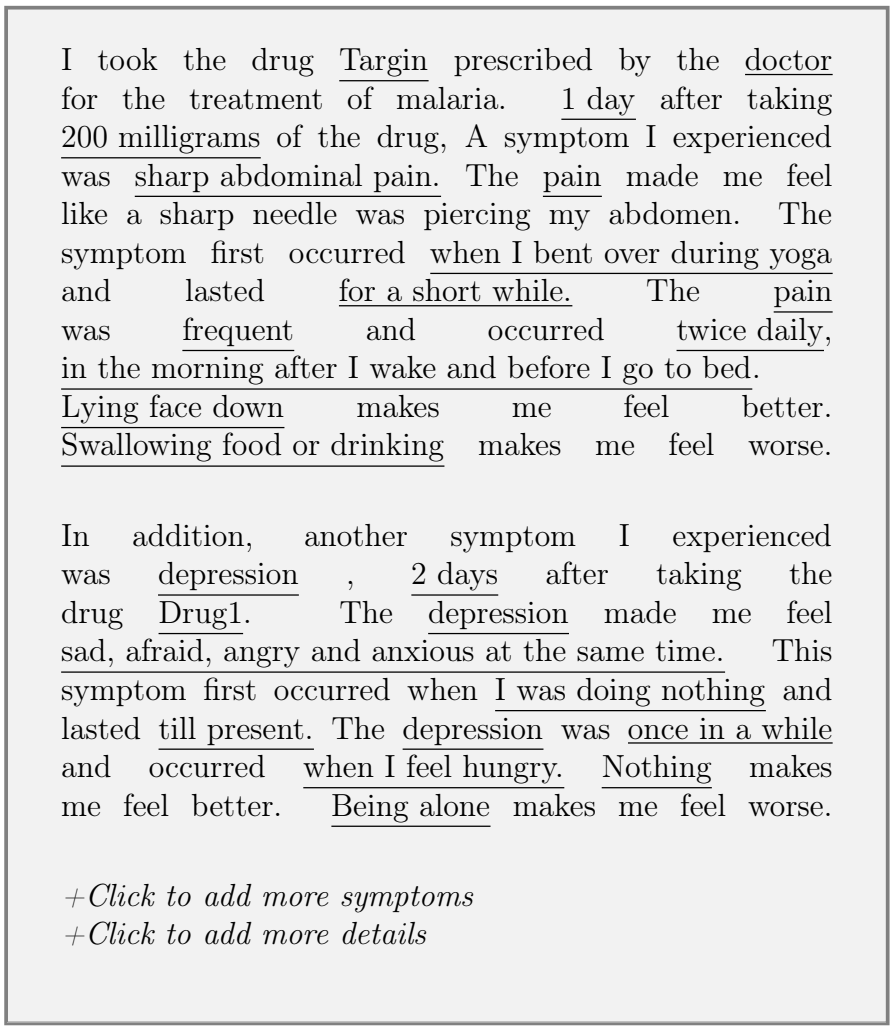

Figure 5.1: Symptom Description Template

The template, captures and addresses all the necessary information required in a basic symptom description.

5.2 Prototype Design

Keeping the architecture shown in Figure 4.3 in mind, we design two prototypes which were web based applications. the technologies used in the realization of the prototype application was HTML,CSS and the Angularjs SPA framework. The design we adopted for the prototype was that of a fill-in-the-blank nature and hence we, from here on, refer to it as such.

The first prototype was a simple web based form much like that of which is available as most current ADR forms online and the second we enhanced to include auto-suggestion and completion. Both forms however were designed with respect to the template we designed.

The data used in the prototype are provided for demo purposes and hence are not actually linked to external data sources. As we explained earlier, the prototype is for demonstration purposes of how the proposed system would to function and how improvements can be measured or observed. Figure 5.2 and Figure 5.3 show a snapshot of the fill-in-the-blank prototype.

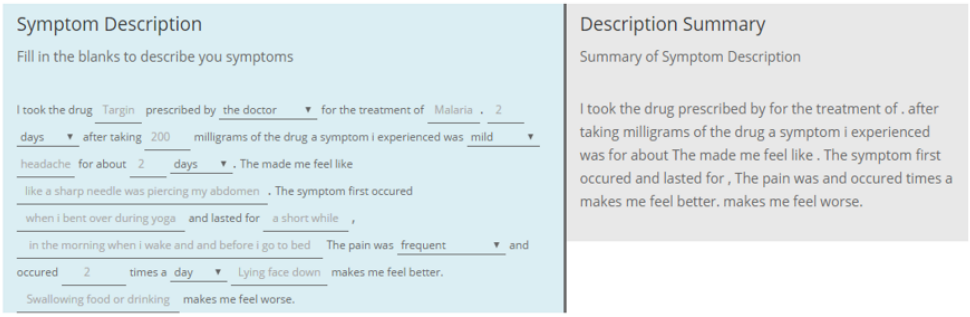

Figure 5.2: Fill-in-the-blanks prototype with placeholders

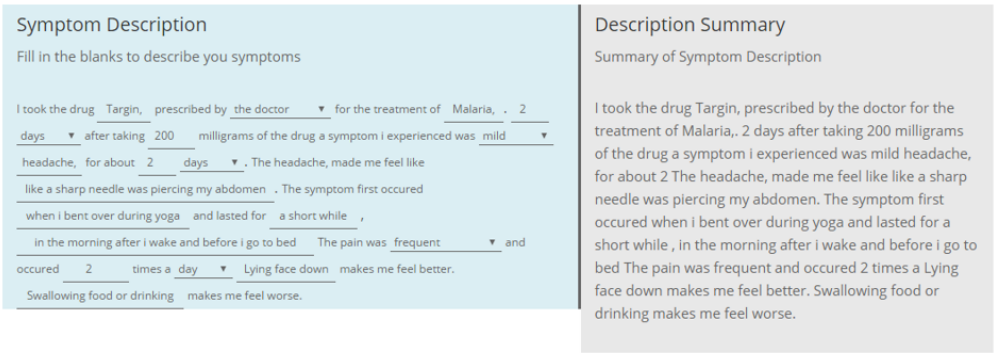

Figure 5.3: Fill-in-the-blanks prototype with description data

5.3 Testing

Up until this point we have conducted research that has led to a theoretical design of a symptom description template, a quality assessment model and

a prototype. There is a need to test our prototype with respect to how it supports our argument on improving ADR reporting. ADR reports are meant for patients or basically anyone with a case to report so it makes sense to test our system with this group. Of course the target group for testing does not involve only reporters but all stakeholders in general.

5.3.1 Scenario based testing

The tests are separated into three different scenarios, all based on our goals and research questions. The first scenario is to illustrate how the symptom description collected through the first survey fits into the prototype we developed. The second scenario is to compare the completeness of the symptom description collected through the survey and those created using the template. The third scenario is to illustrate how the auto-suggestion of the drug names, diseases works.

5.3.2 Scenario 1: Template Expressiveness

The first scenario illustrates how the different types of symptom description collected through the survey described in section 4.2 fits into the template which we have created. For each of the sample symptom description received through the survey, we wrote the description again using the fill-in template. Some of the information that are repeated in the original description are not repeated in the description created using the prototype.

Although the participation to the symptom description survey was less, we received 6-RELIS report which helped us to get an overview of how an actual symptom description in ADR domain would be. In addition to the samples received, we created more sample symptom description to test if it was feasible to write all possible kinds of writing symptom description by a patient using the fill-in technique. Though we cannot assure that we covered all different ways of symptom description by patient, we are satisfied that we had enough samples to test our hypothesis using the prototype created and with the sample descriptions.

To illustrate the test, the screen shot showing the original symptom description and the one that is created using the prototype are attached below. Figure 5.4 shows the original description received through the survey. Figure 5.5 shows the corresponding description created using the fill-in technique.

Flagyl was prescribed by dr for stomach infection. But after taking that tablet for two days I had swelling in my lips which finally ended up with a wound

Figure 5.4: Original Sample symptom Description from Survey

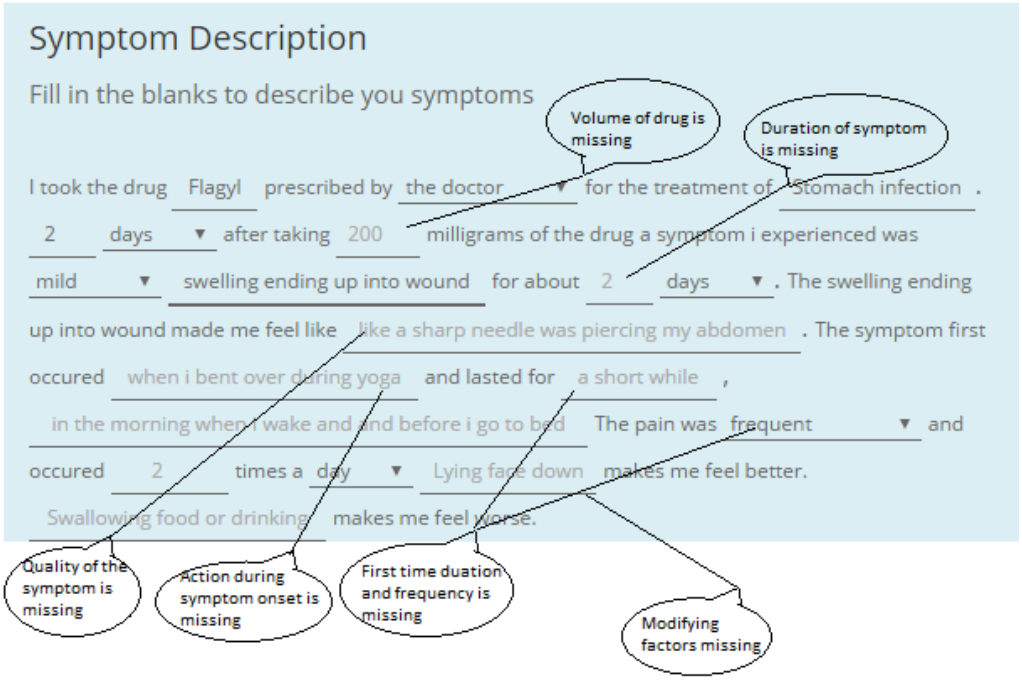

Figure 5.5: Sample description in prototype

The results we obtained from these test indicated that, the descriptions received from the survey could all be expressed using the template. However, in most cases as shown in Figure 5.5, the descriptions failed to include relevant information about time, frequency and duration of symptoms. We suppose that these information will not be missing if the fill-in template is used by the patients to describe the symptoms.

This turn out is to be expected especially because, asking patients to describe their symptoms only is not informative enough. People do not tend to think further than they can understand or see and this is the reason why placeholders, help texts and examples, which are all advocates for the guided reporting concept, are necessary. The template helps the reporters to express themselves and also makes sure that all the necessary information are entered.

It is necessary to mention what makes this different from a normal Q&A form. The argument here is that the design of the template is in a form of a passage that depicts what a description should look like. The design approach intends the template to primarily be in the form paragraph that reporters can modify to suit their description. It is intended to be flexible and simple to use. Also by describing symptoms this way, reporters learn how they are required to describe their symptoms and the level of detail that will suffice for a simple symptom description. This template when used is educative in this sense.

Scenario 2: Completeness of Symptom description

The second scenario is to test the completeness of the symptom descriptions. This test is carried out with the help of the AC3 quality model explained in section 4.1 & 4.5.

Symptom descriptions received through the survey and the RELIS-report are compared with the symptom description written using the fill-in technique. Both the description are compared using the AC3 model and the completeness score for each set are calculated. Each of the factors of symptom description discussed in section 2.6 are evaluated quantitatively and the completeness score is calculated.

Symptom description which are complete with respect to all the information needed will get a higher completeness score whereas those description that misses some details get a less score. This test was to ensure that the quality of the symptom description written using the fill-in technique are more complete and improved compared to the normal free text symptom description by the patients. The more complete the symptom description, the more improved is the quality of the ADR reports.

Though free text has its perks, we find that having a guide such as this while filling in the report helps reporters focus on the aspects of their symptoms that matter and how they are required to express these aspects. Reporters tend to write more when they have a visible example of what is required to be written. The placeholders given in the fields are to help guide reporting and the degree of expressiveness.

Scenario 3: Auto-suggestion of medical terms

The third and final scenario is to illustrate the use of auto-suggestion of the medical terms that includes, drug names, diseases, symptoms etc. The drug name fields are linked to the drug database, the symptoms and disease to SNOMED CT. They can also be implemented by linking them to their respective ontologies which adds more semantic meaning to the different terms representing same disease or symptoms. In the prototype we developed, we did not link to any database or ontologies. We downloaded some part of each and hard-coded in the code. The list is not complete but had a reasonable number to test our hypothesis of saving time and writing semantically meaning sentences across reports.

When the patient starts writing drug names, disease or symptoms in the respective blanks provided in the fill-in template, it will check the database and list all possible matches from which the patient can select the appropriate term. This reduces the spelling mistakes in the drug names, disease name and symptoms and thus makes it more consistent . We characterize this as an improvement in ADR reporting. Figure 5.6 shows the auto suggestion feature the template provides.

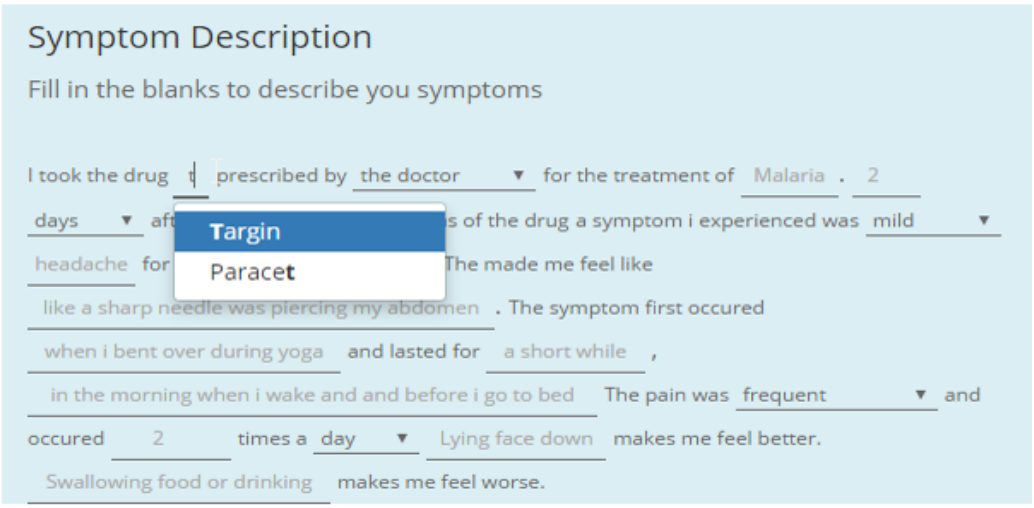

Figure 5.6: The prototype showing the auto-suggest option

5.4 User Test Plan & Design

In order to ascertain the relevance of the work done, there needs to be a user acceptance test and users in this case refers to the stakeholders concerned with the domain.The test is to provide feedback from stakeholders that will help ascertain the usefulness or relevance of our template based symptom description system. The knowledge of how well this system of reporting will integrate into the current methods is vital. Here we introduce a plan and design for how the user acceptance test would be carried out for this system.

5.4.1 Test Content

At the beginning of the test, the medical history of an imaginary patient will be given to the participants in the form of a passage. The passage will be read and interpreted to each participant for clarity. What is required of the participants will then be explained to them and the test will involve a variety of sections.

Section 0: Preamble

This section is where the participants are made aware of what the tasks ahead entail. It will be explained to the participants that they are required to read a passage about a patient and then assume or imagine they were that patient. They were then to express themselves as though they were giving a report on the patient's experiences. The passage would be made available throughout the entire process.

Participants would be informed that everything from the start of the exercise onward would be recorded. They would then be reassured that this was a test of the system and not a personality test, so that they should not be concerned with their own performance. Afterward participants would be encouraged to think-aloud as they execute the tasks and be made aware that the user tasks would proceed without, or with minimal, interruptions from observers. If they were stuck at a task they should always first try to solve the task before asking the observers. In order to help the process of thinking aloud, the participants will be encouraged to read the passages aloud to themselves.

Section 1: Introduction to Passage

Participants will be required to thoroughly read a passage about a patient's medical history. An example of such a passage is as shown in Figure 5.7

Nathan El is a 45 year old male from Trondheim, Norway. He was diagnosed with an ulcer several months earlier. He has lived with this condition without complications for a while.

Nathan's doctor prescribed a new drug X for him to treat the ulcer. He was instructed to take 250 mg of the drug three times daily. The next morning after starting the administration of the drug, Nathan resumed his early morning jogging routine. 20 minutes into his run, he felt a sharp pain in his lower abdomen. In his own words, the pain felt like ants were eating his intestines. He immediately stopped running and crouched. though the pain subsided, it remained. He decided to run it off but that only made it worse. When he got home that morning, he took some pain killer that only helped for a few hours. For two days the pain was mild during the day but got severe in the evening before bed.

Nathan decided to go back to his doctor suspecting he was reacting to the drug he was prescribed.

Figure 5.7: An example of a medical history passage

Section 2: Task

Here the participants are to imagine they are Nathan El and that they had experienced the symptoms he had experienced. This means imagining themselves in Nathan's shoes and describing how they would express their symptoms when asked to report them.

Section 3: Free Text Description

Participants are provided an online form where they are to describe the symptoms they experienced according to the passage in their own words (free text). Participants will not be able to redo this section after moving on to the next section. The reason for this is to avoid the false positive results that may arise. When asked to do a test of this nature, participants may tend to edit sections 3 and 4 to match and that will compromise the results of our experiment.

Section 4: Fill-In-The-Blanks Description

Here, participants describe the same symptoms they described in the previous section using the fill-in-the-blanks template we designed.

It must be noted that we intend to divide the group of participants into two. One group will undertake section 4 before section 3. This is to reduce a bias toward one section.

Section 5: Questionnaire about Task

This section comprises a questionnaire based on the task just completed. It is intended to see how the participants comprehended the tasks and their experiences while using the system

Section 6: Retrospective interview

This part is to allow participants to verbally express their impressions of the whole process.

5.4.2 Recruitment of Participant

For this task, a total of 10 participants between the ages of 18 and 50 years are to be recruited. The choice of the age group is based on the assumption that these group of people are most likely to be computer savvy and have been to the hospital at least once in their lifetime. The system is an online prototype and therefore the participants from the test should at least know how to basically use a computer. The number of participants are limited to a total of 10 because of the need for close observation of how they interact with the software interface. There is no other criteria for participation than that participants are computer-savvy enough to participate in the online task and that they understand the English language at least at a basic level.

5.4.3 Preparation

Before the testing can begin, the computer and english literacy of the participants need to be ascertained. Of course they need not be professional computer engineers or professors in english but they need to understand basic english so as to not misunderstand the questions asked .

5.4.4 Main Tasks

Here participants are given the task after the details are explained to them. They take the tests under observation and the process is both audio and video recorded. The reason for the video recording is to see the expressions on the faces of the participants as they take the tests. Since actions speak louder than words, observers are to keep an eye on the mannerisms of the participants and take note of their expressions.

5.4.5 Post-Test Questionnaire

After executing the tasks, participants are asked through a follow up questionnaire to compare the two systems for describing symptom descriptions. We seek to find out which of the systems the they prefer and why. Also as is to be expected, the fill-in-the-blank method for symptom description entails more underlying backend coding and therefore is susceptible to bugs so we do well to measure effect of this on the user experience.

Participants compare the two methods via a follow up questionnaire we design. The questions in the questionnaire address the experience and impressions the user had while using the system. The questionnaire is shown in Appendix E and covers the following aspects:

Personal Information

Here we collect information on the personal information of participants, including their background and English language proficiency

Participant's Computer Literacy

The computer literacy and especially internet literacy of participants is important for this task therefore we collect information to this regard.

About the Task

We finally seek the opinion of participants about the task and how they found the different methods for describing symptoms. We find out which method they found easier and which they preferred.

CHAPTER 6

Experiments, Results & Discussions

In this chapter we present the results from our experiments and surveys as well as the subsequent analysis and interpretations of our data. As explained earlier, we developed two complementary surveys from with we obtained data relevant to our research into ADR reporting. We present our findings and further discuss their interpretations and how constraints may have affected the findings.

6.1 Symptom Description Survey

Moving on, we explore the AC3 model with respect to symptom descriptions. Symptom descriptions were obtained from two sources. The Norwegian Health Care Authority provided a total of 6 ADR reports from the Norwegian ADR database and the rest of the data was obtained through the survey.

English has become a global language and while most people speak or are learning to speak it, not all have an in depth understanding. This fact is however not very relevant to this domain, in that, the language used in describing symptoms need not be complicated. In fact the simpler the better. We took a multi-national survey in english and acquired and number of symptoms from 5 different nationalities. An obvious observation we made was that most individuals that submitted symptom description used simple english language to express their symptoms.

It is necessary to note that, the language used by patients are significantly different from those used by health professionals. The patient describes the symptoms in the simple form of the language in which they are comfortable with unless the patient themselves are healthcare professionals. For example, the patient describes tiredness and swelling which doctors may interpret as fatigue and oedema. The healthcare professionals make the diagnosis by converting the description of the patients to the corresponding standard medical

labels and then are used for the diagnosis [26]. Though it is not possible for the patient to describe the symptoms in medical terms, the fill-in the blanks technique we propose makes it possible to somewhat describe the symptom completely and accurately, which may help the users of the ADR reports to do a better analysis.

6.1.1 Level of Detail in Symptom Descriptions

The study of the responses received from the survey indicated that participants were generally more interested in listing their symptoms and hardly took time to describe the symptoms they experienced in detail.

6.1.2 Language Structure and Sophistication

As expected, all the participants responded using reported speech and none of them used declarative speech in expressing themselves. The level of sophistication in language we observed was quite low. Participants used simple sentences and tenses to express themselves.

6.1.3 Grammar and spelling

While in the case where the description is human-understandable, the accuracy in grammar would not carry much weight, it is still necessary to indicate that people's susceptibility to spelling errors and misrepresentation of what they intend to convey. We observed that most of the grammatical and spelling errors came from non native English speakers but did not significantly affect the coherence of the description.

6.2 Quality Assessment Survey on Symptom Description Completeness

For this survey we introduce a null hypothesis that suggests that all the basic information required in a symptom description text have the same relevance which can be quantitatively expressed as a single numeric weight value. The participants that took part in the survey were 26 Pharmacists and 20 Nurses .The purpose of the survey was to find out how the health specialists' opinions supported our hypothesis.

Below is a insight into some of the indicators we look out for when grading symptom descriptions. Does the description mention any characteristics of the symptom?

1. Sensation?
    (a) Location of the sensation
    (b) Type of sensation?
    (c) Time of inception and/ duration/ Frequency
    (d) Intensity of sensation?
    (e) Does sensation extend or is it localized?
2. Feelings?
    (a) Intensity of Feelings?
    (b) Location of Feelings?
    (c) Time of inception and/ duration/ Frequency
3. Bodily Functions?
    (a) Type of bodily functions
    (b) Time of inception and/ duration/ Frequency
4. Behavior & Activity?
    (a) Time of inception and/ duration / Frequency

In an attempt to reduce the work involved in formulating a grading scheme for symptoms description, we adopted a hypothesis that grouped symptoms under one of the following categories, thus feelings, bodily functions, sensation and behaviour, but our results proved that this classification is limited. Formulating a grading scale for all symptoms that fall under a single category will not suffice. For instance, Nausea, Headache and Itching are all symptoms that fall under the category sensation. However according to results received from the survey, shown in Figure 6.1, Nausea and headache received low Location grading compared to itching. This is rightly so since for symptoms like Nausea and Headache the location of these symptoms are pretty obvious and hence may not be relevant in a symptom description. For Itching on the other hand, the location of the itchy sensation is of relevance.

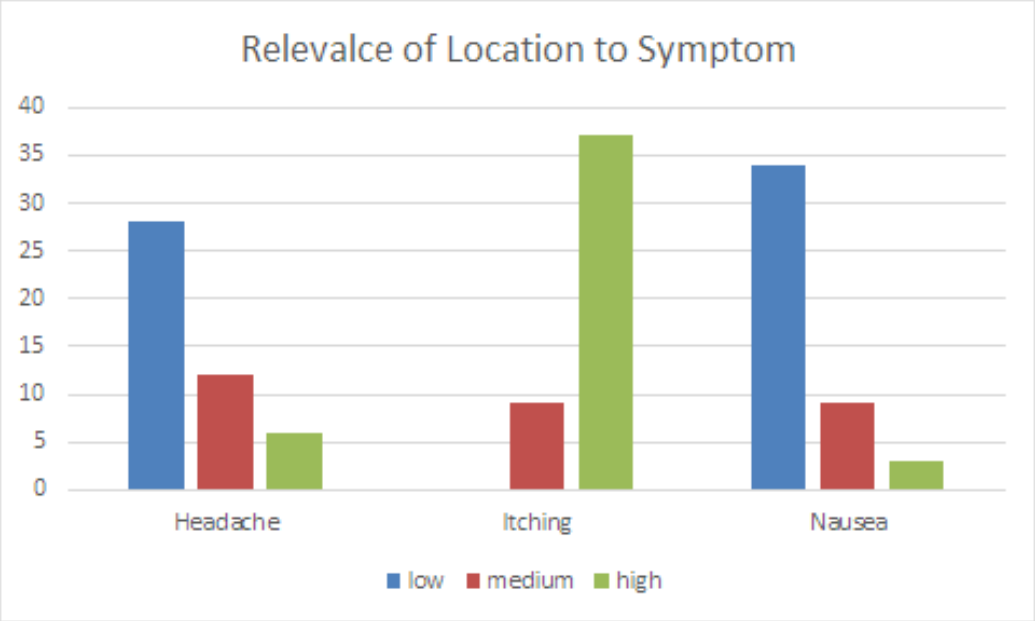

Figure 6.1: Graph of the relevance of Location to Sensation Symptoms

The results therefore suggest that a the classification categories though are relevant, lack the adequate detail to address the disparity between symptoms. Symptom classification is however not a new area of research. According to Sue Meads et al, the advocation of researchers for a uniform standard medical classification terminology for symptoms and medical diagnosis has been the case for a while. They argue that when it comes to symptom coding and classification, such must be viewed in their own light [58], and we could not agree more. According to our work, we find that symptoms can obviously not be classified only under feelings, sensation, behaviour and bodily functions, or at least not on a face value.

The classification of symptoms should be according to the context in which it is to be applied. The quality indicators we use in our survey to formulate the grading system are in themselves a way to classify symptoms that will be relevant to this work. A more extensive survey involving more symptoms will reveal the similarities and differences between symptoms with respect to these factors and hence inform on which symptoms can be assigned similar grades for classification.

Though the classification of the symptoms under the previously suggested categories will not suffice the grading system can still be used on a single-symptom level instead of on a group of classified symptoms.

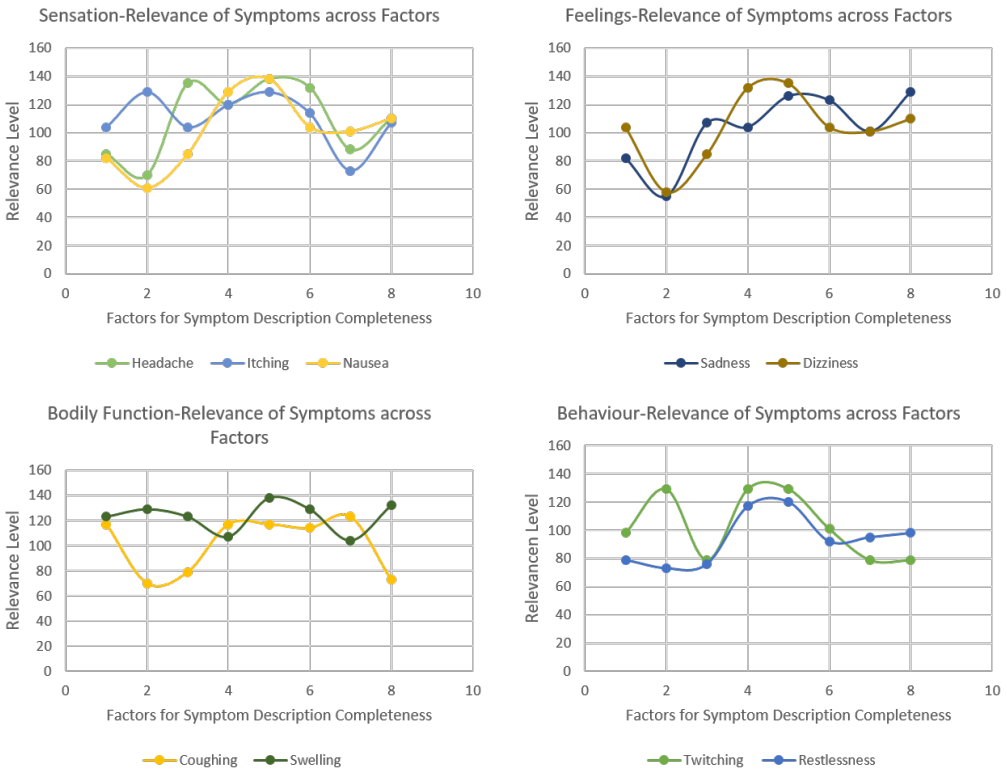

Figure 6.2: Graph Showing Plot of relevance across factors (1:Quality,2:Location, 3:Severity, 4:Chronology & Timing, 5:Manner of Onset, 6:Aggravating & Ameliorating, 7:Co-occurring Symptoms, 8:Suspected Cause)

Figure 6.2 shows the bubble plot of the frequency of relevance on the vertical axis (y-axis) against each completeness factor on the horizontal axis (x-axis). The difference in the pattern of the lines in the graphs above indicate the points where the relevance measure for the symptoms for specific completeness factors vary. We conclude that due to the wide degree of variations at certain factor points, symptoms should be considered in isolation for grading.

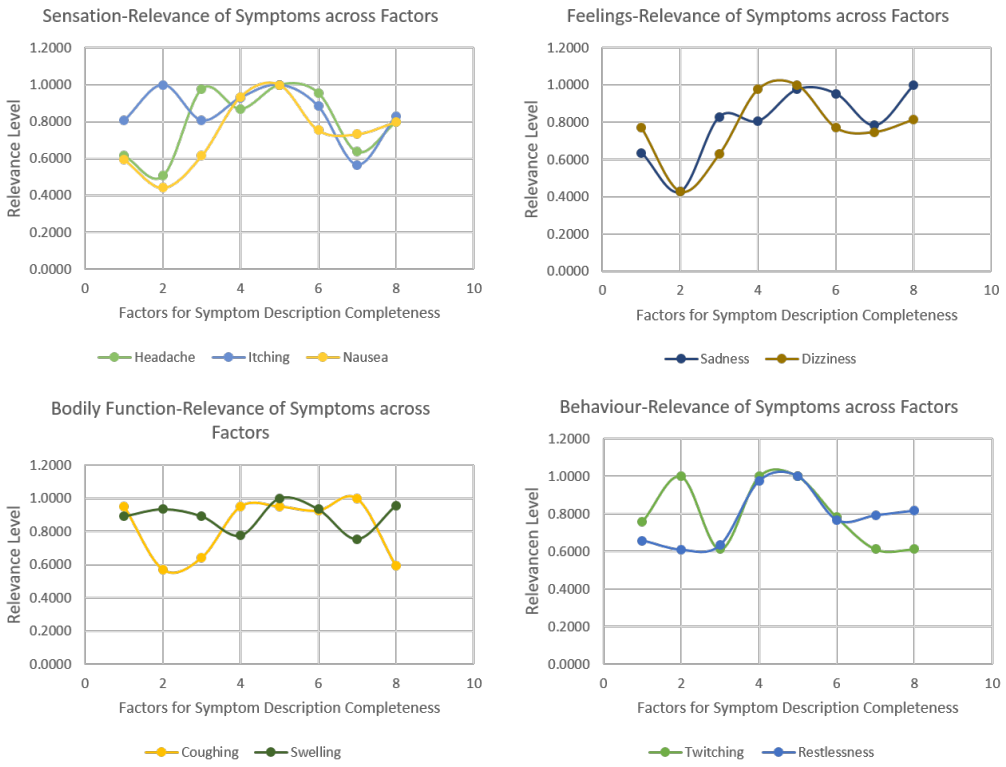

Figure 6.3: Graph Showing Plot of Normalized relevance across factors (1:Quality,2:Location, 3:Severity, 4:Chronology & Timing, 5:Manner of Onset, 6:Aggravating & Ameliorating, 7:Co-occurring Symptoms, 8:Suspected Cause)

For each symptom , we compute the means, normalize them across the completeness factors and use the result to establish the grading scales. The normalized means will serve as the coefficients for grading the completeness of a symptom description text. Figure 6.3 shows the normalized plot. Normalizing the relevance values at the symptom level reveals how health professionals value these information factor with respect to the symptom in question. Table 6.1 shows the coefficient table for grading. Though the table shows a symptom-level grading system the method can be extended to cut across to suffice for classes of symptoms depending on if the context for classification is related to the relevance factors.

Table 6.1: Symptom-Level Grading Coefficients

	Quality	**Location**	**Severity**	**Chronology & Timing**	**Manner of Onset**	**Aggravating & Ameliorating**	**Co-Occurring Symptoms**	**Suspected Cause**
Headache	0.616	0.507	0.978	0.87	1	0.957	0.638	0.797
Sadness	0.636	0.426	0.829	0.806	0.977	0.953	0.783	1
Coughing	0.951	0.569	0.642	0.951	0.951	0.927	1	0.593
Twitching	0.76	1	0.612	1	1	0.783	0.612	0.612
Itching	0.806	1	0.806	0.93	1	0.884	0.566	0.829
Nausea	0.594	0.442	0.616	0.935	1	0.754	0.732	0.797
Dizziness	0.77	0.43	0.63	0.978	1	0.77	0.748	0.815
Swelling	0.891	0.935	0.891	0.775	1	0.935	0.754	0.957
Restlessness	0.658	0.608	0.633	0.975	1	0.767	0.792	0.817

The coefficients in Table 6.1 establish a relative gradient between the basic factors required in a symptom description for a single symptom. It suggest that the relevance of said information are not necessarily the same. The relevance health professionals place on information in symptom descriptions do not carry the same weight. We therefore base our grading system on this finding and grade symptom descriptions according to the quantitative values in the table.

6.2.1 Kolmogorov-Smirnov Goodness-of-Fit Test

The Kolmogorov-Smirnov test is used to decide if a sample comes from a population with a specific distribution. The two-sample Kolmogorov-Smirnov test is a nonparametric hypothesis test that evaluates the difference between the cumulative distribution frequencies (cdfs) of the distributions of the two sample data vectors over the range of x in each data set [65]

$$D^* = \max x(\hat{F}1(x) - \hat{F}2(x)) \tag{6.1}$$

where,
$\hat{F}1(x)$ is the proportion of x1 values less than or equal to x and
$\hat{F}2(x)$ is the proportion of x2 values less than or equal to x.

We use the kolmogorov-smirnov goodness of fit function provided by MATLAB [65] to compare the curves shown in Figure 6.4. Results from his test show a stronger degree of similarity between symptoms across the different symptom categories (thus sensation, feelings etc) which goes to further disprove the initial basis for classifying symptoms under such categories. We compare the normalized relevance frequency values for symptom as shown in the Figure 6.4 below using a significance value of 5%. We use MATLAB tool to compute these values.

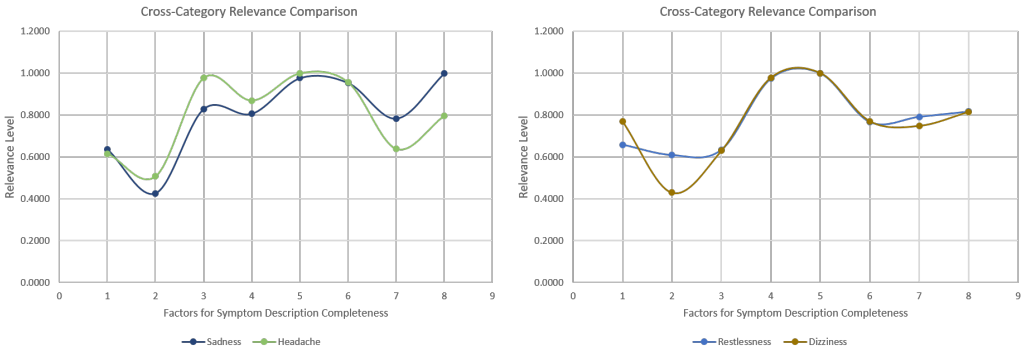

Figure 6.4: Comparing Cross-Category Symptoms

Though the symptom pair; Restlessness and Dizziness and Sadness and Headache, belong to different categories, they show a stronger degree of similarity than symptoms in the same category. The relevance of this comparison and analysis is to establish that symptoms with a high degree of similarity can be given similar quantitative grades for description completeness.

6.3 Assessing Symptom Descriptions

Using the coefficients in Table 6.1 Above, we can grade the quality of symptom descriptions quantitatively with respect to completeness.

Let's take a look at a sample symptom description retrieved from our survey,

> *'Flagyl was prescribed by dr for stomach infection. But after taking that tablet for two days I had swelling in my lips which finally ended up with a wound.'*

Flagyl is one of the brand names that Metronidazole is marketed under. The reporter is clearly more familiar with the brand name for the drug than its real name. This is an example of how many different terms can refer to the same concept. 'Metronidazole' could have easily been put in place of 'Flagyl' and unless both terms compute to the same semantic value we would term such a description inconsistent. It is quite obvious that the term 'dr' as used in the text refers to 'doctor' however the reporter chooses to use a short version of the term. Like the sample above, majority of the description submitted were quite short and lacked much detail. Yet however deficient, none

can be said to have had irrelevant information with regards to symptoms.

Table 6.2: Category-Level Grading Coefficients

Symptom Category	Symptom	Total Relevance Score	Average Category Score
Sensation	Headache	6.363	6.351
	Itching	6.821	
	Nausea	5.87	
Feeling	Sadness	6.41	6.2755
	Dizziness	6.141	
Bodily Function	Swelling	7.138	6.861
	Coughing	6.584	
Activities & Behavior	Twitching	6.379	6.3145
	Restlessness	6.25	

Despite the fact that we have disproved the hypothesis that supports classifying symptoms under the aforementioned categories for the purposes of uniform grading, we nevertheless go ahead to do so for demonstrative purposes. This is because there are symptoms that are present in the sample data received from the survey that we did not address in our grading experiment. So in order to use a uniform grading scale for all symptoms, we use the category level relevance values to demonstrate how the grading will be done otherwise.Table 6.2 shows the category level coefficients.

The above description mentions the symptom 'swelling' and hence is expected to get a symptom-level completeness score (ComS) of 6.861 units. A description as such will get a Completeness score of 2.826 according to our grading scale which implies about 40% completeness. Our method for grading treats symptoms in isolation and hence does not assume any relationship between them. This approach is in tandem with the subsequent template we developed for symptom description that isolates and retrieves symptoms separately and addresses their qualities in isolation. This is not to say that symptoms are not related but the that conclusion is not for the patient or reporter to draw.Given all the information regarding the symptoms a patient feels, health professionals are in the position of drawing the relationships between symptoms. While this approach for symptom description is not conventional due to the fact that reporters are more susceptible

to draw their own conclusions and report on those conclusions.

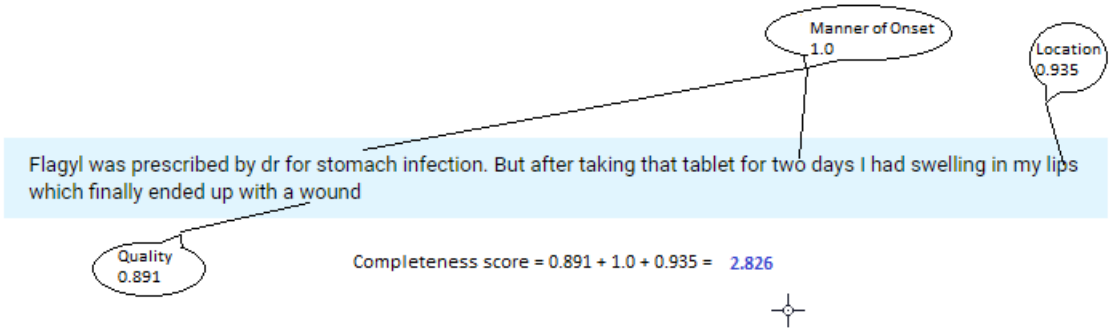

Figure 6.5: Symptom Description - Example 1

We evaluated the completeness of the sample symptom description received and the completeness score of the symptom descriptions lay between 0.7612 units and 5.0085 units. None of the description received through the survey has got a 100% completion score.

In example1, the description is about the symptom "swelling" grouped under "Bodily Function". As per our AC3 model, Table 6.2, symptoms that are grouped under Bodily Function are expected to have a completeness score of 6.861 units but on an average. As you can see in Figure 6.5, the completion score of a symptom description that can be grouped under Bodily function received just 2.826 units indicating that it is 64% less complete than expected. On an average, description of symptoms under this category received through the survey has a completion score of 2.605 units, 37.97% of the information needed are present.

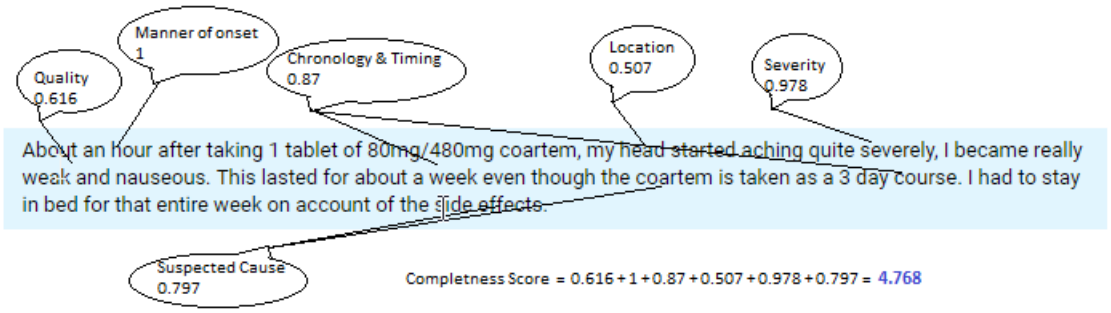

Figure 6.6: Symptom Description - Example 2

In the same way, another example shown in Figure 6.6 shows that the completion score is 4.768. This is an example that can be grouped under Sensation which is expected to have 6.35 units. However, on an average, descriptions received under this category has a completion score of 1.728 units as most of them just wrote the symptoms that got. Though the example is 75.09% complete, in general this category is found to be 27.2% complete.

The completeness score of descriptions under "Feelings" on an average is 1.126 units which is 17.94% complete. In order to be 100% complete, the score should be 6.2755 units. The completeness score of descriptions under "Feelings" on an average is 2.434 units which is 38.55% complete.

From the results,it is found that symptom description that fall under the category "Bodily function" is more complete than those under other categories. However none of them are complete.The results are attached in AppendixD

6.4 Limitations

Although we are satisfied with the experiments and results, there were some limitations during the experiments that are worth noting.

6.4.1 Survey Participation

It was little difficult to predict the survey response earlier. We expected more than 75 responses but received only 46 responses. Attempts to make an appointment with medical teams that work on the ADR report proved futile even after repeated follow-ups. This indeed affected the survey response rate. However we received quite a good number of response from the pharmacists

and nurses. It would have been ideal to have responses from such a team since they work directly with ADR reports.

6.4.2 Time

The thesis duration is 21 weeks. Some of the surveys and experiments we did needed more time for follow-up and took more time than planned. Also, there were some legal issues in getting the ADR reports from the Norwegian Medicines Agency. The approval process had taken more time and we received only 6 anonymized ADR reports.

6.4.3 No adequate sample symptom description

We had no symptom description sample during the initial analysis. It was difficult getting sample RELIS forms. The team needed to get approval from Ministry of Health, Norway in order to share the reports with us. Upon getting approval we received only 6 reports in Norsk. This influenced the decision to make a survey of our own. The responses we received were less than expected. Even after repeated follow-ups.

6.5 Fill-In-The-Blanks Template Design

In this section we present and discuss the design we propose for the fully-fledged symptom description template and highlight relevant aspects that enable a more interactive human-computer interaction. In this project we implemented a mock up of the design but here we discuss into more detail the features of the system when fully realized. The motivation behind the proposal of the fill-in-the-blanks template was to take away the natural language complication that come with dealing with free text so long as symptom description is concerned.

The proposed system is a software system meant to interact with humans so in our attempt to introduce the features we refer to the ISO 9126-1 Quality Model for software architecture and adapt it to the current domain. Table 6.3 shows the characteristics of the ISO 9126-1 Quality Model.

Table 6.3: The ISO 9126-1 Quality Model

Characteristics	Description
Functionality	The capability of the software product to provide functions which meet stated and implied needs when the software is used under specified conditions (what the software does to fulfill needs)
Reliability	The capability of the software product to maintain its level of performance under stated conditions for a stated period of time
Usability	The capability of the software product to be understood, learned, used and attractive to the user, when used under specified conditions (the effort needed for use)
Efficiency	The capability of the software product to provide appropriate performance, relative to the amount of resources used, under stated conditions
Maintainability	The capability of the software product to be modified. Modifications may include corrections, improvements or adaptations of the software to changes in the environment and in the requirements and functional specifications (the effort needed to be modified)
Portability	The capability of the software product to be transferred from one environment to another. The environment may include organizational, hardware or software environment

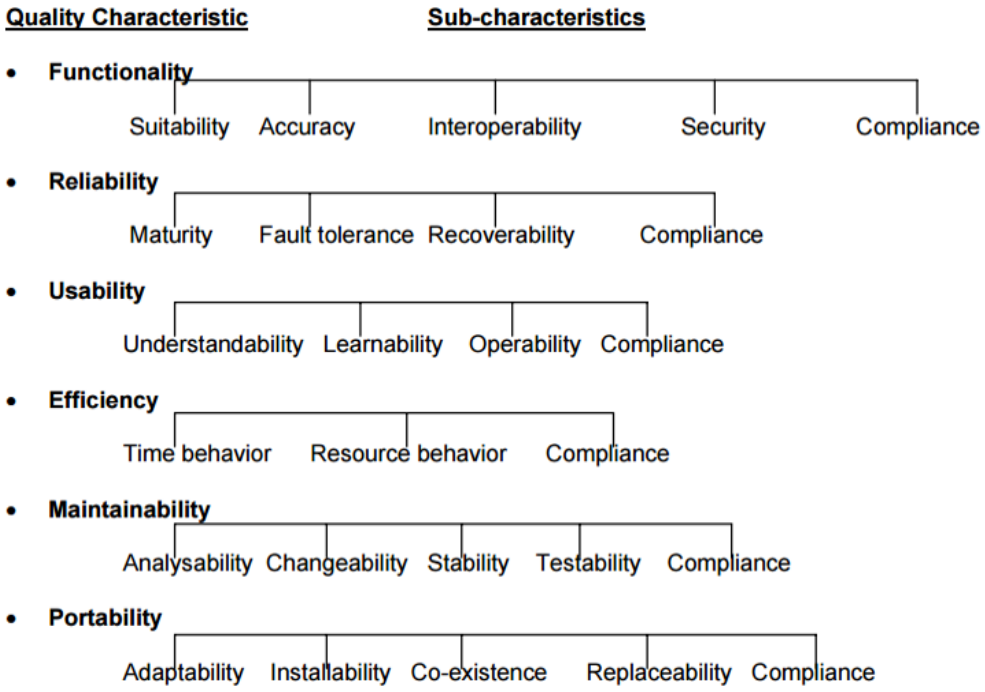

Figure 6.7: Sub-characteristics of ISO 9126-1 Quality Model

6.5.1 ISO Standard Compliance

In this section, we describe some of the features of the fill-in-the-blanks system from the ISO standard perspective. Though not all the sub-characteristics apply we describe the system from the perspective of those that do. The proposed system needs to be compliant to the ISO 9126-1 Quality Model as shown in Figure 6.7.

This section contains the requirements for the system to be developed using the fill-in blank technique. The system to be developed is the Adverse Drug Event Reporting System that supports auto-suggestion of the drug names, disease and symptoms.

1. **Functional**

   - **Suitability:**The system would have an auto suggest and completion feature for relevant medical terms as well as other enhanced user experience features. A guided feature that helps the patients write symptom description in machine readable form like the sentences that can be parsed using the ATEMPTO parser. It should

do exactly what it is intended to do and meet the needs of the stakeholder of the system.

- **Accuracy:**The patient history details have to be pulled from the EHR. The patient's Norwegian ID can be used as the primary key field. The symptoms fields are to be linked with symptoms ontology so that the different ways in which a symptom can be expressed are linked and are also machine readable. The disease fields are to be linked with the disease ontology that makes the reports machine readable and are also linked to medical vocabularies through mapping of SNOMED, MeSH etc. All these features have to do with access to data therefore it makes sense that the level of accuracy is needed in retrieval of the data that is intended; otherwise there is hardly a point in its realization.
- **Security & Compliance:**They system need to be secured and the patients data needs to be protected as per the Personal Health Data Filing System Act(Act of 18 May 2001 No. 24 on Personal Health Data Filing Systems and the Processing of Personal Health Data). The system should also prevent anonymous access.
- **Interoperability:**The ADR report details are to be sent to EHR and the patient's history details are needs to be retrieved from EHR enabling interoperability between ADR system and EHR system. Data storage and exchange formats as well as authentication routs are considered here.

2. **Reliability**

- **Fault tolerance:** The system should be able to allow disease name, drug name and symptoms that are not auto-suggested so that the patient is not frustrated. In theses cases, they can be corrected by the person processing the reports in the next level. All systems have a tolerable margin of error that can pass and this system should be no exception. A failure in any of the modules that will make up the system should not imply a total system breakdown. This is the reason for adopting a modular approach to system development.
- **Recoverability:** In case of software update failures, the system should be able to restore to the previous version of the system. The system should be able to restore the data in case of corruption. The system should be able to provide a secondary lower end version until the primary version is fixed.

3. **Usability** The user interface of the application is the most important requirement for the reporters. It should be user friendly, the focus of attention where much information is needed should be readily seen.

    - **Understandability:** The reporters need to be able to understand the system easily and they should be able to write the reports without any hazzle. The help texts, hints etc. helps the users to understand what is expected from them.
    - **Learnability:** Every new system the is introduced comes with an inherent learning curve. The learning curve of the system needs to be turnable. Reporters need not struggle to understand how to use the system. The design of the system must support easy learning.

4. **Efficiency**

    - **Time Behavior:** The system response time and the processing time should be efficient. The data retrieval time should be optimum.
    - **Resource Behavior:** The system need to use the resources optimally and appropriately.

5. **Maintainability**

    - **Changeability:** The system should be able to support updates to the software and changes to any modules without issues.
    - **Stability:** The system need to be stable during the maintenance activities. The system should be able to capture unexpected behaviors
    - **Testability:** The system should allow testing of the updated individual components without modifying other components.

6. **Portability**

    - **Adaptability:** The system should be compatible to different browsers and different operating systems. Changes to the data structure of the data resources should have minimum effect on the system.
    - **Replaceability:** A smart way to design the system is to build it incrementally. New features can be added with time to replace old ones after alpha and beta testing processes have been conducted.

6.6 The Fully Fledged Application

We give an overview of the vision behind our proposed application and mention some of the features that should be readily implementable and updatable.

6.6.1 Auto-Completion and Suggestion

The vision for the auto completion and suggestion features go beyond the provision of dropdown fields in the form. Rather than just showing a drop down list of matched terms, there should be mini descriptions associated with these terms that inform reporters of the underlying semantic option. This task is more than just the selection of the best matched term but rather advocates the selection of the terms that the reporter actually intended to mention. Work must be done on similar, misleading or ambiguous terms in order for this process to work.

6.6.2 The Free-Text Feel

One argument we do well to mention are the advantages of free text input with regard to expressiveness and flexibility. The realization of this feature requires advanced user experience design coding. For instance one feature that free text fields have is the ability for text to wrap-around. We envision the fill-in-the-blank template to be similar in that input fields are able to wrap-around seamlessly while maintaining the passage structure of the description text.

6.6.3 Aesthetics & Interactivity

This aspect is typically referred to as look-and-feel and it cannot be underestimated or overlooked. On the topic of ADR reporting and symptom description, elegance in the design of the software interface is especially important if reporting is to be encouraged.

An elegant software design can promote confidence in the system. It is quite well known that one's ability to use technological devices with pleasure, confidence and fluency depends on their ability to build a cognitive or conceptual model of the device's behavior. Let us consider our fill-in-the-blank proposal. There is a special need for considering elegance in tandem with functionality. The vision for the system is quite complex and therefore stands the risk of misleading or frustrating users. Bruce [66] argues that an effective cognitive model of a system is not required to reflect its actual

operations or internal structure but must be accurate enough to not mislead users; thus resulting in a loss of confidence and frustration. In this case in particular where we attempt to propose an elegant middle ground between free text and conventional forms fields, user frustration is a major concern.

An intelligible dynamical structure in an elegant design can help users to form an effective cognitive model. In this case where users would reports alongside interactive auto-completion and suggestion features as well as pop-up help texts, a cognitive model helps users not get lost. Thorough elegance, the use of the fill-in-the-blank system would be graceful and the learning curve that usually leads to user frustration will be less steep.

6.6.4 Beyond Symptom Description

It is necessary to state that the ideas we propose in this work go beyond symptom description. These generally apply to all free text fields in the ADR reporting form. Where there is free text, we hope to apply these techniques. The bigger picture has to do with ADR reporting as a whole and this includes consideration for EHR records data and how the ADR forms inter-operates with EHR systems. Though we focus on one part, the picture is much bigger.

CHAPTER 7

Conclusion

This chapter comprises the conclusion of our work toward further study. The objective of this research was geared toward improving ADR reporting and reports. After research into the ADR reporting area we acquired knowledge on the area which lead to the development and proposal of our AC3 Model for Symptom Description Quality Assessment. Based on this model we perform an evaluation of data received from a survey we conducted and build an insight into ADR reporting from the perspective of non medical professionals. We further drill down further and look into the Completeness of symptom descriptions according to a quantitative measure developed through the conduction of a survey where health professionals grade the relevance of some basic information required in symptom descriptions with regard to the symptom under consideration.

In the course of this project, we have tried to answer the research questions in Chapter1, section1.3.

G1: *Research on the state-of-the-art of the symptom description.*

The background theory of the clinical process and the ADR reports are presented in Chapter2 and in the section3.2, we presented the state-of-the-art of the ADR reporting and their quality and about the symptoms description.

G2: *Develop a quality assessment model based on the following quality indicators; completeness, consistency, correctness and adequacy.*

We developed a quality assessment model AC3 and the model is presented in section4.1. The evaluation of the parameters are presented in section4.5.

G3: *Is the quality(with respect to the measures discussed above) of reports and reporting process improved using controlled language in symptom*

description?

This question is proved with the help of the results. From the results we find that where the fill-in template is employed, the completeness of the symptom description according to measures we predefined increases; thus contributing to the completeness of the reports. Linking of the field to drug databases and disease ontologies increases the semantic richness of the reports. Despite the obvious challenges, we somewhat interpret this as an improvement in the overall quality of the reports.

The idea of an improved ADR reporting is a holistic concept. This means that, it can be tackled by improving its constituent sub aspects. Symptom description is a vital part of the whole ADR reporting system and it quality affects the relevance of ADR reports as a whole. In correspondence with efficient links to relevant EHR data and efficient data extraction and loading processes, the improvements to symptom description as we present it plays its role in promoting the wider goal.

CHAPTER 8

Future Works

In this chapter we propose and discuss the further studies that can be done based on our work as well as improvements that can be made to the current work. This thesis work span a duration of 22 weeks and coupled with numerous unforeseen challenges in the acquisition of data relevant to our work as well as the challenges with soliciting participants for experiments. In spite of these constraints, we present some recommendations and suggestions in tandem, that can be done to further improve this work and the ADR reporting domain as a whole.

8.1 Verbalizing Symptom Descriptions in First Order Logic

First order logic is a formal language that computers can relate to and process. This is an area yet to be researched into; where symptom descriptions are verbalized in the form of a formal computer interpretable language like FOL. One such tool that harnesses the power of first order logic in text is the Attempto Controlled English Framework (ACE). The text below shows how a symptom description can be verbalized in the ACE language.

Ordinary Text:
'Flagyl was prescribed by doctor for stomach infection. But after taking that tablet for two days I had swelling in my lips which finally ended up with a wound'

ACE Verbalization:
Flagyl is prescribed by the doctor for the infection in the stomach....

According to the rules of Attempto Controlled English, and ACE text can either be a specification, a query, or an instruction or in other words declarative, interrogative or imperative respectively [67]. It is evident that symptom description texts usually take a descriptive form and much like all the other text data retrieved from our survey, usually come in the form of reported speech and therefore are in the past tense . Of Course it should be expected that when an individual is asked to report an adverse event, they would describe such event in the past tense. Verbalizing text in this way has its advantages in the sense that it is possible to perform reasoning operation on the text and also query the text for data. Queries such as "Who prescribed Flagyl" and "What is prescribed" are possible in this case.

This realistic phenomenon adds another task to the free text processing problem that involves converting said descriptions to declarative present tenses. In order to make the text parsable by ACE, there is a need to convert the past-tensed descriptive text to a present-tensed declarative one otherwise ACE with its current limitations will fail to parse the text. The rationale behind our proposal here is that queryable and reasonable data is usually useful data.

8.2 Improving visualization effect of fill in the blank form

All manner of software produced are usually produced for a target group of consumers. Consumers are the customers that patronize the software regardless of its intended function. One thing common to consumers is their appreciation of look-and-feel. For a piece of software, the look-and-feel otherwise known as the user experience plays a vital role in whether the software will be patronized or not.

In the case of our proposed fill in the blank method for symptom description, the template should provide a user experience that is seamless with the way an ordinary reporter will type in their symptom description information into a free text box. This is particularly important for pharmacovigilance in the sense that ADR reporting response improvement cannot be unmarried from the willingness of patients to report. A form that gives reporters more work than they can tolerate will not auger well for the ADR reporting campaign. This is where the 'illusion' of visual appeal comes in. In section6.6.3, we address the issue of aesthetics in the design of the system interface.

8.3 Improving the Grading system

In this thesis, we grouped the symptoms in four categories:- Sensations, Feelings, Bodily behaviors, and Activities. An example of two symptoms from each category were graded by the Healthcare professionals for relevance with respect to the different symptom description factors. Based on the survey results, we created a grading scale for each of the group. These grading system of the symptoms could be improved either by using the NAMCS coding schema [57] or by individually grading the relevance of each factors with respect to the symptom.

Further, we propose and discuss ways that the broader adverse drug reaction reporting can be improved. Regarding improvement, we look at aspects of reporting that affect time taken to report, report content and level of participation from both patients and health professionals. Currently, many countries employ form-based reporting methods in ADR reporting and such countries include UK, US, India and New Zealand. There are some areas that can be looked at to improve such reporting.

8.4 Identifiable Patients

One category of information that all adverse drug event forms have in common is the patient's personal information. Though the exhaustiveness of data collected may vary across adverse drug reaction forms in different countries, all suggest that personal patient information data like name, age, gender etc are required in reporting of ADR. We argue that reporters need not enter such personal information anytime they need to make a report, In the case of reporting by healthcare professionals like general practitioners, information about patients can be extracted from electronic health records where available.

In Norway for instance every person studying or working can register with a GP as long as he or she has the Norwegian identity number. GPs prescribe medicines and provide referral to specialists or hospitalization, if necessary [68]. The existence of such an infrastructure makes it possible to link adverse drug events to national records. This way general practitioners who fill ADR forms should not have to manually enter the patient data.

Furthermore, extraction of patient information alone is not sufficient for the purposes of progressive analysis. Instead of just extracting information and filling ADR forms to make the reporting faster, a persistent link should be

kept between the report and the health record so that if details of the personal information change, there will be no need to update the ADR report. Of course there may not be a need to update the ADR report at all regardless of whether patient's information changes overtime but the idea here is to ensure that the same patient is being referred to. Also the health of the patient after reporting the ADR may be monitored in relation to the ADR report to find out if the reaction has influenced patient's weight or allergic reactions overtime. This gives room for progressive analysis of reports over time for a given patient.

8.5 EHR Interface for Information Exchange

There are challenges with the extraction of information from health records in the sense available a single source of electronic health records or an interface that links to all that if a single national ADR form is used by the governing body, there must either be available health record databases. In the case of the latter, the multiple EHRs must be synced in such a way that they support the extraction of the most up-to-date information relevant for the ADR report.

8.6 Interactivity in Reporting

This aspect may increase participants' willingness to report as an interactive online form may be more interesting to fill compared to a static online form or worse yet a paper based form. Interactivity here can be in the form a Q&A reporting where the reporter is guided through the reporting process by through interactive questioning and answering. Another way of interaction could be the identification and emphasis of drugs, drug-groups and even DDI in the report; suggested DDI's can be extracted from free-text portions of the report and proposed to the reporter for confirmation. Identifying DDIs this way, by machine extraction complemented with confirmation form reporter would be better than using only machine extraction methods.

8.7 Combined professional & patient reporting

Up until now we have discussed patient reporting in contrast with reporting by health professionals and highlighted their strength and weaknesses [69]. Perhaps it is a better idea to view these two reporting sources as complementary. If patients and health care professionals report on a specific patient's reaction to drugs are synced as one report, then it will be easier to track

patient's reaction to drugs from over time from different practitioners' perspectives. This idea encourages reporting of adverse drug reaction or events of a specific patient over time and by different practitioners as one document. Of Course this proposes a centralized information system structure for ADR reporting and though may come with its challenges, its advantages can perhaps offset these challenges.

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APPENDIX A

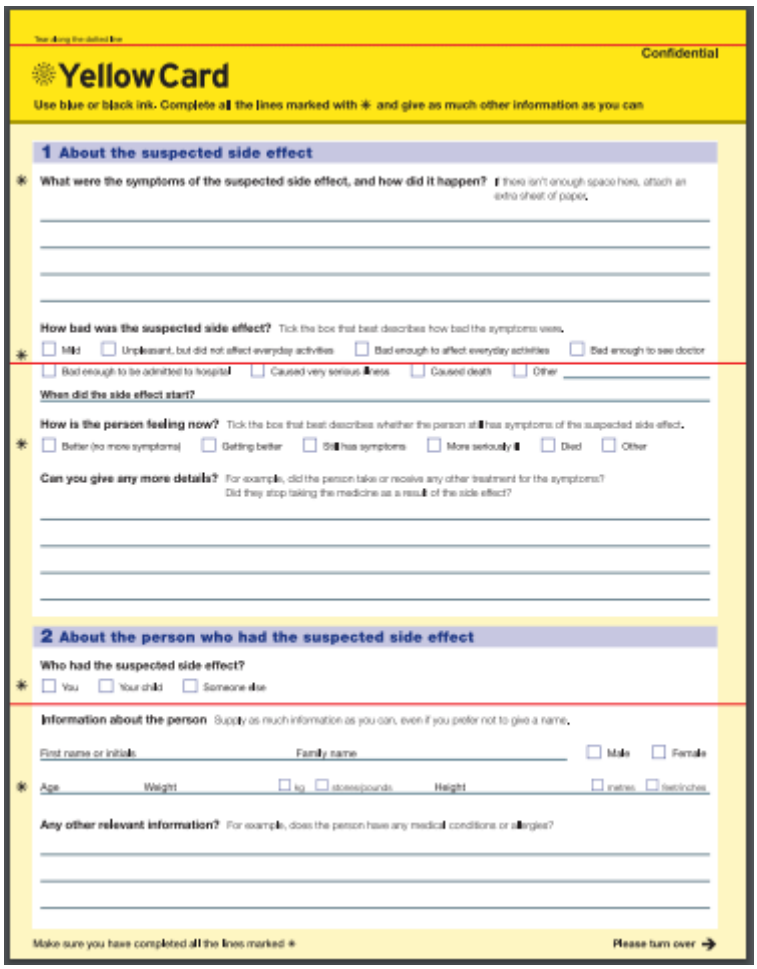
Links to ADR reporting forms of selected countries

S.No	Country	Link
1	Denmark	https://blanket.laegemiddelstyrelsen.dk/Forms/ESUSARForm/ReportDetails/?languageid=1
2	UK	https://yellowcard.mhra.gov.uk/yellowcards/reportmediator/
3	New Zealand	https://nzphvc.otago.ac.nz/report/
4	India	http://www.cdsco.nic.in/writereaddata/ADR%20form%20PvPI.pdf
5	USA	http://www.fda.gov/Safety/MedWatch/HowToReport/default.htm
6	Australia	https://www.tga.gov.au/report-side-effect-medicine
7	Singapore	http://eservice.hsa.gov.sg/adr/adr/adrOnline.do?action=loadOnlineForm

APPENDIX B

British YellowCard Reporting Forms

B.1 Member of Public YellowCard Reporting Form



Confidential

YellowCard

Use blue or black ink. Complete all the lines marked with ✱ and give as much other information as you can

1 About the suspected side effect

✱ **What were the symptoms of the suspected side effect, and how did it happen?** If there isn't enough space here, attach an extra sheet of paper.

How bad was the suspected side effect? Tick the box that best describes how bad the symptoms were.

✱ ☐ Mild ☐ Unpleasant, but did not affect everyday activities ☐ Bad enough to affect everyday activities ☐ Bad enough to see doctor
☐ Bad enough to be admitted to hospital ☐ Caused very serious illness ☐ Caused death ☐ Other

When did the side effect start?

How is the person feeling now? Tick the box that best describes whether the person still has symptoms of the suspected side effect.

✱ ☐ Better (no more symptoms) ☐ Getting better ☐ Still has symptoms ☐ More seriously ill ☐ Died ☐ Other

Can you give any more details? For example, did the person take or receive any other treatment for the symptoms? Did they stop taking the medicine as a result of the side effect?

2 About the person who had the suspected side effect

✱ **Who had the suspected side effect?** ☐ You ☐ Your child ☐ Someone else

Information about the person Supply as much information as you can, even if you prefer not to give a name.

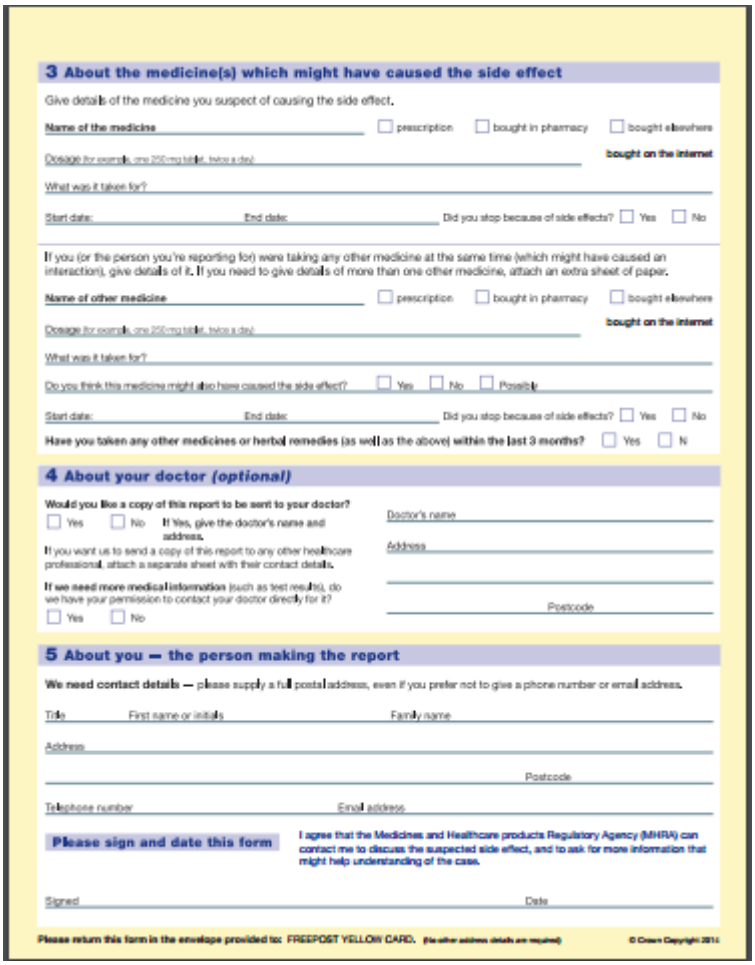
First name or initials Family name ☐ Male ☐ Female

✱ Age Weight ☐ kg ☐ stones/pounds Height ☐ metres ☐ feet/inches

Any other relevant information? For example, does the person have any medical conditions or allergies?

Make sure you have completed all the lines marked ✱ Please turn over

Figure B.1: Member of Public YellowCard Reporting Form - Page 1



3 About the medicine(s) which might have caused the side effect

Give details of the medicine you suspect of causing the side effect.

Name of the medicine ☐ prescription ☐ bought in pharmacy ☐ bought elsewhere

Dosage (for example, one 250mg tablet, twice a day) **bought on the internet**

What was it taken for?

Start date: End date: Did you stop because of side effects? ☐ Yes ☐ No

If you (or the person you're reporting for) were taking any other medicine at the same time (which might have caused an interaction), give details of it. If you need to give details of more than one other medicine, attach an extra sheet of paper.

Name of other medicine ☐ prescription ☐ bought in pharmacy ☐ bought elsewhere

Dosage (for example, one 250mg tablet, twice a day) **bought on the internet**

What was it taken for?

Do you think this medicine might also have caused the side effect? ☐ Yes ☐ No ☐ Possibly

Start date: End date: Did you stop because of side effects? ☐ Yes ☐ No

Have you taken any other medicines or herbal remedies (as well as the above) within the last 3 months? ☐ Yes ☐ N

4 About your doctor *(optional)*

Would you like a copy of this report to be sent to your doctor?
☐ Yes ☐ No **If Yes, give the doctor's name and address.**

If you want us to send a copy of this report to any other healthcare professional, attach a separate sheet with their contact details.

If we need more medical information (such as test results), do we have your permission to contact your doctor directly for it?
☐ Yes ☐ No

Doctor's name

Address

Postcode

5 About you — the person making the report

We need contact details — please supply a full postal address, even if you prefer not to give a phone number or email address.

Title First name or initials Family name

Address

Postcode

Telephone number Email address

Please sign and date this form

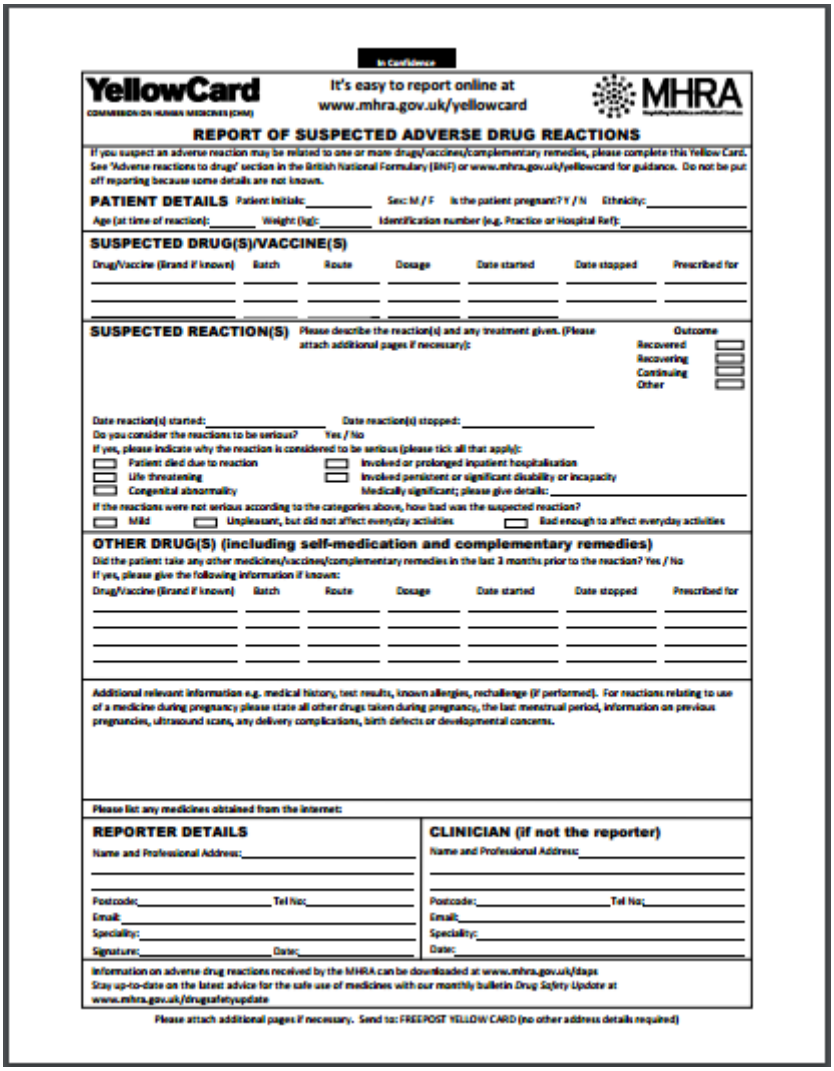
I agree that the Medicines and Healthcare products Regulatory Agency (MHRA) can contact me to discuss the suspected side effect, and to ask for more information that might help understanding of the case.

Signed Date

Please return this form in the envelope provided to: FREEPOST YELLOW CARD. (No other address details are required) © Crown Copyright 2014

Figure B.2: Member of Public YellowCard Reporting Form - Page 2

B.2 Healthcare Professional Yellow Card Reporting Form



In Confidence

YellowCard
COMMISSION ON HUMAN MEDICINES (CHM)

It's easy to report online at
www.mhra.gov.uk/yellowcard

MHRA

REPORT OF SUSPECTED ADVERSE DRUG REACTIONS

If you suspect an adverse reaction may be related to one or more drugs/vaccines/complementary remedies, please complete this Yellow Card. See 'Adverse reactions to drugs' section in the British National Formulary (BNF) or www.mhra.gov.uk/yellowcard for guidance. Do not be put off reporting because some details are not known.

PATIENT DETAILS Patient initials: _____ Sex: M / F Is the patient pregnant? Y / N Ethnicity: _____

Age (at time of reaction): _____ Weight (kg): _____ Identification number (e.g. Practice or Hospital Ref): _____

SUSPECTED DRUG(S)/VACCINE(S)

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for

SUSPECTED REACTION(S) Please describe the reaction(s) and any treatment given. (Please attach additional pages if necessary):

Outcome
Recovered ☐
Recovering ☐
Continuing ☐
Other ☐

Date reaction(s) started: _____ Date reaction(s) stopped: _____

Do you consider the reactions to be serious? Yes / No

If yes, please indicate why the reaction is considered to be serious (please tick all that apply):

☐ Patient died due to reaction
☐ Life threatening
☐ Congenital abnormality
☐ Involved or prolonged inpatient hospitalisation
☐ Involved persistent or significant disability or incapacity
Medically significant; please give details: _____

If the reactions were not serious according to the categories above, how bad was the suspected reaction?

☐ Mild ☐ Unpleasant, but did not affect everyday activities ☐ Bad enough to affect everyday activities

OTHER DRUG(S) (including self-medication and complementary remedies)

Did the patient take any other medicines/vaccines/complementary remedies in the last 3 months prior to the reaction? Yes / No

If yes, please give the following information if known:

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for

Additional relevant information e.g. medical history, test results, known allergies, rechallenge (if performed). For reactions relating to use of a medicine during pregnancy please state all other drugs taken during pregnancy, the last menstrual period, information on previous pregnancies, ultrasound scans, any delivery complications, birth defects or developmental concerns.

Please list any medicines obtained from the internet:

REPORTER DETAILS

Name and Professional Address: _____

Postcode: _____ Tel No: _____

Email: _____

Speciality: _____

Signature: _____ Date: _____

CLINICIAN (if not the reporter)

Name and Professional Address: _____

Postcode: _____ Tel No: _____

Email: _____

Speciality: _____

Date: _____

Information on adverse drug reactions received by the MHRA can be downloaded at www.mhra.gov.uk/daps

Stay up-to-date on the latest advice for the safe use of medicines with our monthly bulletin *Drug Safety Update* at www.mhra.gov.uk/drugsafetyupdate

Please attach additional pages if necessary. Send to: FREEPOST YELLOW CARD (no other address details required)

Figure B.3: Healthcare Professional Yellow Card Reporting Form

APPENDIX C

Symptom Description Quality Assessment Survey

Symptom Description Quality Assessment

This brief questionnaire is intended to support a research into improving the Quality of Symptom Description in Adverse Drug Reaction (ADR) reporting by patients. In ADR reporting, reporters (patients) usually describe their symptoms in free text. According to our research so far, It stands that there are basic information needed for effective analysis of symptoms.

Please carefully read and tick the appropriate boxes.

Quality Assessment

Below, we identify some basic Information needed for effective analysis of symptom. Given that the following basic information are present in a symptom description text, grade each basic content according to how relevant it is to the listed symptoms. Relevance in this case is interpreted as the usefulness of the information in contribution to effective analysis of the symptom.

The factors are described in more detail below and include:
Quality of the symptom
The complete and concise description (feelings, sensation, bodily functions etc.) of the symptom.

Location of the symptom: The area of the body where symptom is located.

Severity of the symptom: This is the description of the intensity of the symptom

Chronology and timing of the symptom: Symptom frequency and timing.

Manner of onset: How the symptom started and patient state before it started.

Aggravating & Ameliorating Conditions: What make the symptom better or worse?

Co-occurring symptoms: Other symptoms that co-occur with the main symptom being described.

Suspected Cause: What the patient suspects is the cause of the symptom.

1. Professional Occupation?

a. **General Practitioner**
b. **Nurse**
c. **Pharmacists**
d. **Other** _____

2. Department : _____

3. Tick or shade ONE of the boxes indicating the information's degree of relevance to the stated symptom's description.

FACTORS / SYMPTOMS	Quality of Symptom Complete and concise description of the symptom			Location of symptom Area of the body symptom is located			Severity of symptom Symptom intensity			Chronology, Frequency &Timing Symptom frequency and timing		
	Degree of Relevance To Symptom											
	Low	Med	High	Low	Med	High	Low	Med	High	Low	Med	High
Headache												
Sadness												
Coughing												
Twitching												
Itching												
Nausea												
Dizziness												
Swelling												
Restlessness												

FACTORS / SYMPTOMS	Manner of onset How the symptom started and patient state before it started			Aggravating & Ameliorating Conditions What make the symptom better or worse			Co-occurring Symptoms Other parallel symptom			Suspected Cause Cause suspected by Reporting Patient		
	Degree of Relevance To Symptom											
	Low	Med	High	Low	Med	High	Low	Med	High	Low	Med	High
Headache												
Sadness												
Coughing												
Twitching												
Itching												
Nausea												
Dizziness												
Swelling												
Restlessness												

Comments?

Save this form and send to yehonatq@stud.ntnu.no

APPENDIX D

Symptom Description Completeness Evaluation

NO	Symptom Description	Symptom Category	Completion Score								
			Quality	Location	Severity	Chronology & Timing	Manner of Onset	Aggravating & Ameliorating	Co Occurring Symptoms	Suspected Cause	Final score
1	Flagyl was prescribed by dr for stomach infection. But after taking that tablet for two days I had swelling in my lips which finally ended up with a wound	Bodily function	0.891	0.935	-	-	1	-	-	-	2.826
2	After two days i started with loose motion, loss of appetite and i had to stop taking the tablets.	Bodily function	--	-	-	-	0.9755	-	-	-	0.9755
3	Three hours after taking Naclofen, i experienced general body weakness and also felt drowsy. hence had to sleep all day.	Feelings	--	0.428	-	-	0.9885	-	-	-	1.4165
4	I got headache, constipation and dry mouth	Sensation, Activities & Behavior	--	-	-	-	-	-	-	-	0
5	After 4 hours of taking a single dose of Artesunate Amodiaquine I experience dry mouth and constant thirst, weakness and light headedness	Feelings	--	-	-	0.892	0.9885	-	-	-	1.8805
6	took 2 tablets of paracetamol on empty stomach. i had uncomfortable feeling in my stomach as if had stomach ulcer	Bodily function	0.709	0.804	-	-	-	-	-	0.7145	2.2275
7	Makes me drowsy	Feelings	-	-	-	-	-	-	-	-	0
8	Around one hour later of taking the antibiotics, I got dizzy and several headaches, after the first and half week of treatment I presented abdominal/stomach pain	Feelings	-	0.428	-	0.892	0.9885	-	-	-	2.3085
9	Few weeks after taking acne drugs I felt dryness and irritation in the skin. Sometimes I felt skin itches, burns, peels, and stomach upset. Although drugs effect was positive for acne, the side effects caused worry. I decided to meet my GP to discuss this matter.	Feelings	0.703	-	-	-	0.9885	-	0.7655	-	2.457
10	About an hour after taking 1 tablet of 80mg/480mg coartem, my head started aching quite severely, I became really weak and nauseous. This lasted for about a week even though the coartem is taken as a 3 day course. I had to stay in bed for that entire week on account of the side effects.	Sensation,Feelings	0.616	0.507	0.978	0.87	1	-	-	0.797	4.768
11	A day after I to Artesunate Amodaiquine, I became far more sick than when I went to the hospital. I felt very dizzy, weak, loss of appetite and could not even move. I couldnt sleepand i was restless	Feelings, Behavior &Activities	0.706	-	-	-	0.99425	-	0.73375	-	2.434
12	Dizziness, uncontrollable sleep	Feelings	-	-	-	-	-	-	-	-	0
13	I took Peri-DS. After arounf 30 minutes i started vomitting. I feel like vomitting the whole day. I was better next day.	Bodily function	-	-	-	0.863	0.9755	0.931	-	-	2.7695
14	Dizziness and nausea	Feelings	-	-	-	-	-	-	-	-	0
15	While intaking ibuprofin , the kid has got pain in the stomach . It happened because during fever he didn't ate food and he had the medicine in empty stomach three times a day. But as per the prescription one can intake the medicine only after having some food.	Sensation	-	0.65	0.8	-	-	-	-	0.808	2.258
16	Five days after taking fertility tablets, i got bloating, severe shortness of breath. Got admitted immediately. Was in ICU for 5 days. After 5 days, i was better	Bodily function	-	0.752	0.7665	0.863	0.9755	-	-	-	3.357
17	I took Diane 35 and I started feeling tired.	Feelings	-	-	-	-	-	-	-	-	0
18	Triaz is prescribed to me for treating acnes. A week after taking the tablets i noticed redness in the skin follwed by itching. I stopped the medicine and got advice from the doctor immediatley	Sensation	-	-	-	-	1	-	0.645	-	1.645
19	When i took iron suppliments for the first time, I experienced diaheria for almost a day.	Bodily function	-	-	-	0.863	0.9755	-	-	-	1.8385
20	I am taking Lisinopril for blood pressure. When i started with the drug i got frequent cough that was fine with time. 2 months back i started getting dry cough and doctor gave an alternative drug.	Bodily function	-	-	-	0.863	0.9755	-	-	-	1.8385
21	I had a side effect of stmach pain for 3 days after taking the medicine.	Sensation	-	-	-	0.892	-	-	-	-	0.892
22	Dizziness and vomiting	Feelings	-	-	-	-	-	-	0.7655	-	0.7655
23	Skin dryness and irritation	Bodily function & Sensation	-	-	-	-	-	-	0.7612	-	0.7612
24	My uncle had been prescribed for thyroid with thyronorm 50 mcg. A month after taking the taking tablets he noticed that he is lossing weight more rapidly. When he contacted the doctor, it was found that it was a side effect to thyronorm. He has been given an alternative medicine(forgot the name).	Bodily function & Sensation	-	0.78325	-	-	0.98775	-	-	-	1.771
25	Eye redishness & severe yellow pus in both eyes for more than a month after using eye drops meant for curing infection. During night when i sleep, the pus was more and was not able to open the eyes in the morning.	bodily function	0.921	0.752	0.7665	0.863	-	0.931	-	0.775	5.0085

APPENDIX E

Post-Test Questionnaire

Thank you for participating in our experiment. Welcome to the post-text questionnaire. Tell us what you think about the task and whether you found the systems usable. What are your impressions of the Fill-In-The-Blanks method for symptom description in comparison to that of free text description. Read the following questions carefully and provide the appropriate and honest response. Thank you

About You

1. **How old are you?** I am _____ years old.
2. **Gender?**
   - ☐ Male
   - ☐ Female
3. **Nationality?** I am a _____.
4. **Do you speak and/or write English?**
   - ☐ Yes
   - ☐ No
5. **English Language Proficiency?**
   - ☐ Beginner
   - ☐ Intermediate
   - ☐ Native
6. **What is your occupation?**
   - ☐ Student
   - ☐ Health Worker
   - ☐ Engineer or Scientist
   - ☐ Researcher
   - ☐ Other _____

7. Which education is the highest you have completed?

- ☐ Primary school (7-10 years)
- ☐ Secondary school
- ☐ Collage / university, less than 4 years
- ☐ Collage / university, more than 4 years

Your Computer Literacy

8a. Are you computer savvy?

- ☐ Yes
- ☐ No

8b. If Yes, how good are you at using computers? not good ☐—☐—☐—☐—☐ excellent

9. Are you familiar with the internet?

- ☐ Yes
- ☐ No

10. How often do you use the internet?

- ☐ Never to once a week
- ☐ 1 to 3 times a week
- ☐ 3 to 5 times a week
- ☐ Every day

11. Have you ever filled-in an Online Form?

- ☐ Yes
- ☐ No
- ☐ Don't know

12a. Have you ever filled-in an Adverse Drug Reaction (ADR) Form?

- ☐ Yes
- ☐ No
- ☐ Don't know

12b. If yes. What type of form was it?

- ☐ Paper Based Form
- ☐ Online Form
- ☐ Both

About Task

13. Please describe your first impression about this task.

_____

_____

_____

_____

14. Did you understand what you were supposed to do?

□ Yes

□ No

□ Maybe

15. How difficult was this task? easy □—□—□—□—□ impossible

16. How would you prefer to describe you symptoms?

□ By free Text

□ By Filling in a form

□ I don't like describing symptoms

17. Which of the section in the task did you think helped you describe your symptoms better?

□ Free Text Section (Section 3)

□ Fill-In-The-Blanks Section (Section 4)

□ I don't like describing symptoms

18. Which of the sections would you prefer to describe you symptoms?

□ Free Text Section (Section 3)

□ Fill-In-The-Blanks Section (Section 4)

□ None

19. What was your impression of Fill-In-The-Blanks Section (Section 4)

_____

_____

_____