5. Summary and Conclusion

Drugs help patients by aiding in diagnosis, prevention or curing ailments but the down side is that drug itself results in morbidities either with improper use or sometimes even with appropriate use. The adverse reaction monitoring systems had their birth after the landmark event of thalidomide disaster. In the Indian context even though awareness on adverse drug reaction monitoring is increasing, there is no permanent national level comprehensive program to cover all aspects of detection, evaluation, documentation of ADRs. Documentation and analysis of ADRs provide number of valuable information on incidence, pattern, risk factors, predictors, and economic impact on health care. This study was aimed to study the number of aspects on ADRs like development of indicators for ADEs, study the pattern, causality of ADRs in different departments like Medicine, Dermatology and Cardiology and develop prediction models for the severity and cost of management of ADRs in certain departments.

There are number of ways to monitor ADEs and the use of ADE indictors to screen them provides an alternative method for detecting them. An initial list of ADE indicators based on published literature was developed by a panel of three experts. The list of indicators' was subjected to review by a Delphi panel of 5 members. The Delphi panel reviewed the list of valid indicators and also suggested an addition of new indicators. The final list of indicators was used to review 100 previously documented adverse drug event case reports. The case reports were screened for the presence of any of the indicator from the list. The parameters like number of indicators per case report and the most used indicators were studied. From the literature 72 item indicator list was initially prepared which was further narrowed down to a list of 63 items. The Delphi panel conducted review with these 63 items. At the end of review after addition and deletion of indicators, a 49 item indicator list was finalized. When this list of indicators was used for the review of adverse drug event case reports, 42 indicators were identified. On an average 3 indicators were present in the reviewed case reports. An indicator list was developed for identification of adverse drug events in the study setup. The relevance of this indicator list was demonstrated by the presence of these indicators in the previously documented
adverse drug event reports. The developed indicators’ list may be prospectively tested in screening case records for detection of ADEs. When this tool is used to screen large number of records, it can be validated and upgraded suitably. This tool has a potential to be used as a screening tool for electronic records thereby enhancing detection of drug related harm to patients. This tool will assist in intensive monitoring of patients in medicine departments for potential ADEs and once ADEs are detected, they can be investigated further to assess the causality and document as ADRs.

Intensive monitoring was carried out in one medicine unit of the study hospital. The aim of this work was to study the pattern, drugs involved, severity, outcomes and preventability of adverse drug reactions using intensive monitoring approach. Prospective, intensive monitoring was carried out over a period of 6 months. The WHO definition of ADR was adopted. Standard scales were used for assessing causality and severity. Drugs involved, predisposing factors and outcomes of the reactions were studied. The overall incidence of ADR was 17.11% (246/1438). In the intensively followed group of 1438 patients, 2.57% (37) of patients were admitted due to ADRs. Incidence of ADRs during hospital stay was 14.53%. Type A reactions accounted for 82.3% of the ADRs. Using the Naranjo algorithm, 194 (61.19%) ADRs were assessed as ‘probable’ whereas 120 (37.86%) were assessed as ‘possible’ and 3 (1%) were classified as ‘definite’ in relation to the suspected drug. In 22.08% of ADRs, the reaction was considered to be preventable (definitely or probably preventable). Anti-bacterials (J0- WHO-ATC level 2) were the most common drug class associated with ADRs documented (94; 27.62%). Gastro-intestinal system was the most common organ system affected (62; 19.56%). The most frequently reported reaction was Hepatocellular damage (38; 11.99%). The incidence of ADRs documented in this study was higher than those studies reported from similar study set up. Many of the reported studies used spontaneous reporting approach which was usually associated with lower rates of reporting. Use of intensive monitoring approach based on active surveillance of records might be helpful in better detection and documentation of ADRs.
The cost involved in the management of ADRs was reported to be US $ 2.6 to 150 in previous reports from India. The aim of the current work was to study the cost associated with documented adverse drug reactions in the medicine department of the study hospital. Data of intensive monitoring study was used to assess the cost of management of ADRs. Cost of management per adverse reaction was found to be Rs.4,945 (US$ 115). The prediction model for the cost of management of ADR was developed and validated using suitable statistical methods. The developed model identified key predictors like investigation charges, length of stay and professional charges which contribute to the overall cost of management. When the developed model was used for prediction of cost in another data set the intra class correlation was found to be good. The limitation of the present model is that it was developed based on the cost pattern of the study hospital and it needs to be tested in a large dataset to enhance its prediction. Once this model is validated using large datasets, it has potential application in predicting the overall cost of management of ADRs.

A statistical model to predict probability of developing severe ADRs was developed based on intensive monitoring data from medicine department. Traditionally linear regression is used to model risk. Generalized Linear Models are increasingly being used as a tool in binary outcome situation like whether severe ADRs develop or not. The present work was aimed to develop a model for prediction on development of severe ADRs using Generalized Linear Modeling approach.

The associated risk factors for development of severe ADRs were obtained by means of a multiple logistic regression model. Backward elimination procedure was used for selection of variables. Hosmer-lemeshow test and area under the ROC curve (AUROCC) was used to test the goodness of fit of the model. The 5% significance level was used when assessing factors for model inclusion.

The risk factors considered significant for ADRs were age, gender, number of drugs taken, having disease like infectious disease and diseases of respiratory tract, organ system involved and taking drugs like antibiotics. The final model for predicting severe ADR, \[ \log(p(y=1)/(1-p(y=1))) = 1.78+0.28*(age \text{ 30-40}) - 1.3*(age>45) + 0.45 * (Onset - Latent) - 0.722 * (Onset -Sub-acute) + 2.17 * (LOS 3-6 days) + 1.54 * (LOS}
> 6 days) + 0.46 * (gender - Male) + 0.58 * (ATCgp-A1) - 0.22 * (ATCgp-C0) + 1.55 * (ATCgp-J0) + 3.42 * (ATCgp-M0) + 1.12 * (ATCgp-N0) - 14.36 * (ATCgp-P0) - 0.54 * (ATCgp-R0) + 2.39 * (ATCgp-others) - 0.63 * (OS - CNS) - 0.63 * (OS - GIT) + 2.51 * (OS - liver and biliary) - 1.04 * (OS - metabolic and nutritional) + 0.04 * (OS - skin & appendages). Where, \( P(y=1) \) = Probability of having severe ADR given the covariates. Covariates were: LOS- Length of stay; ATC- Anatomical Therapeutic Chemical (ATC) classification- level 2; OS- Organ system involved.

The developed model for prediction of ADR was validated using area under the ROC curve which had a value of 0.83 far higher than the required value of 0.7. This model was developed to answer the question on the probability of manifesting a severe ADR when the patient develops an ADR. This model will help to predict the severity of a reaction during initial stages of developing ADR, thereby potentially helping in deciding management strategy for a particular patient.

Using models to predict cost and severity of ADRs is attempted in the present work to explore the potential of this approach in the clinical settings. Although these models need further validation using large datasets, they provide a platform for further development of these concepts and take them to the level of implementation in clinical settings.

Retrospective study on the ATT-IH was carried out to identify the clinical characteristics which are risk factors for the development of hepatotoxicity. Case records of 941 patients diagnosed with tuberculosis infection with clinical and biochemical follow up were screened. ATT-IH was identified in 45 (4.78%) out of 941 patient records screened. Almost 60% of patient had normalization of their LFT within 2 weeks of cessation of anti TB therapy. No recurrence of ATT-IH was observed after reintroduction of therapy. The number of males and females who had reactions was almost similar. Hepatotoxicity was severe in pulmonary tuberculosis and age more than 35 years. Alcohol use, Lower BMI, Concurrent use of Pyrazinamide was identified in more number of patients in the group with ATT-IH. The current study identified the presence of number of risk factors in patients with ATT-IH. The limitation of this study was it did not analyze the data of all patient records screened to identify ATT-IH. Such analysis might have helped to carry out a
case control comparisons using multiple logistic regressions to establish the risk factors for ATT-IH unambiguously.

Intensive monitoring work was carried out in one unit of dermatology department and in units where cases of cutaneous reactions were referred / transferred to dermatology department. This study was designed to study the pattern and cost involved in the management of cADRs in hospitalised patients. The present prospective intensive monitoring study was carried out for a period of six months. Causality, Preventability and severity were assessed using suitable scales. The cost incurred in managing the documented ADRs was calculated based on the total amount spent on the patients with ADR divided by total number of patients with ADRs.

142 cADRs from 108 patients was reported. More reports of ADR were documented for anti-bacterials for systemic use (76; 53.52%) followed by anti-epileptics (17.61 %) and anti-inflammatory agents. Ceftriaxone produced the highest number of reactions (15; 10.56%) followed by ciprofloxacin (13; 9.15%). The most frequently reported reaction was maculo-papular rashes (80; 56.34%) followed by Pruritis (10, 7.04%0 and urticaria (9; 6.34%). Using the Naranjo algorithm, 86 (60.6%) cADRs were defined as ‘probable’ whereas 47 (33.1%) were defined as ‘possible’ and 8 (5.6%) were classified as ‘definite’ in relation to the suspected drug. The total cost incurred in managing all cADRs reported was Rs. 367,692 (US$ 7993.30). The minimum cost incurred for managing cADRs was RS 39 (US$ 0.84) and the maximum cost incurred was Rs.64,663 (US$ 1405.72) . Ten patients had severe reactions and incurred the highest expenditure, with an average cost of Rs. 17,428 (US$ 378.88) each. The average cost of managing an ADR at the hospital was found to be Rs. 3404 (US$ 74). Cutaneous reactions are normally mild in nature with most of the reactions treated by outpatient departments of dermatology department. This study focused on the in-patient units to identify the cADRs in this group of patients and calculate the cost of management of cADRs in this group. Since this study had patients from the dermatology department and patients with cutaneous reactions from other department like medicine, the total number to include in denominator was
unclear; therefore calculation of incidence of cADRs could not be performed in this group.

Intensive monitoring of ADRs in cardiology department was carried out. Patients with cardiovascular disease are particularly vulnerable to ADRs due to their advanced age, polypharmacy, and the influence of heart disease on drug metabolism. The potential of ADR for a particular cardiovascular drug varies with the individual and disease being treated, and the extent of exposure to other drugs. Studies show that cardiovascular drugs are among the most common cause of ADRs in hospitalized patients. This study was aimed to estimate incidence and pattern of ADRs in patients admitted in cardiology unit and to identify the predictors for developing ADRs in cardiology patients using Generalized Estimation Equation.

All patients admitted in the cardiovascular unit during an eight months period (Feb to Sep 2009) were evaluated for cardiovascular drug related ADRs. All ADRs were suitably assessed. During 8 month study period, a total of 757 patients, 431 men and 326 women, using cardiovascular medications were intensively monitored. 241 patients (31.84%) including 122 females and 119 males reported at least one ADR. A total number of 388 ADRs were detected. Age group of >60 years developed more ADRs compared to other age groups. The most frequent system-organ classes affected by ADRs were Platelet, bleeding & clotting disorders (188, 48.89%), Metabolic and nutritional disorders (5313.66%) and Gastro-intestinal disorders (50, 12. 89%). The strategy for the management of ADRs was drug withdrawal (94.3%) and dose alteration (5.4%). Aspirin produced the highest number of reactions (150; 38.7%) followed by heparin (45; 11.6%), atorvastatin (24; 6.2%) and ramipril (24; 6.2%). 85.31% of ADRs were categorized as probable followed by 7.99% as definite and 6.7% as possible. 64.4 % patients recovered from the ADRs and 35.6 % were recovering during discharge.

Multivariate logistic regression analysis showed that the patients of age >60 years, female gender, alcoholics and smokers habits and those taking more than 7 drugs were at a higher risk of experiencing an ADR. Age was also an important risk factor in preventable and serious ADRs. The calculated incidence was higher than many reported studies. The current study identified the common ADRs and their predictors
in patients taking cardiovascular medications. These predictors help to identify patients who are at increased risk for ADRs and therefore can be monitored intensively and adopt suitable measures to minimize or prevent ADRs.

In conclusion, the present work was planned and executed to study the multiple dimensions of ADRs in hospitalized patients in a south Indian hospital. The indicator tool developed in the study has potential to be used as a tool in screening records for potential ADEs in medicine department. The intensive monitoring of ADRs in medicine wards helped to assess the incidence and pattern of ADRs. From the same set of data; models for predicting cost and probability of severe ADRs were developed and validated. These predictive models are an attempt to use such methodology in the clinical settings with potential benefits. Combined with indicator tools, these predictive tools provide an opportunity to identify potential ADRs and predict its severity and cost. From a retrospective data from tuberculosis patients the clinical characteristics of patients with ATT-IH was studied. Many of these characteristics of patients were reported as risk factors for the development of hepatotoxicity. Pattern and cost of cADRs were assessed. Similarly incidence, pattern and predictors of ADRs were studied in cardiology patients. The collected data on ADRs from medicine and other departments gave a picture on ADRs in these departments. The developed predictive models highlighted the potential applications of this approach in this discipline.