2. Review of Literature

2.1 Acute Coronary Syndrome

Acute coronary syndrome consists of three acute myocardial ischemic states such as unstable angina, non-ST elevation MI and ST elevation MI. In ST elevation MI, persistent ST segment elevation is seen whereas in case of non-ST elevation infarction ST segment, elevation is generally absent in ECG. Unstable angina is a clinical stage between stable angina and acute MI.

2.1.1 Epidemiology of ACS

Unstable angina and non-ST segment elevation MI account for about 2.5 million hospital admissions worldwide and are a major cause of morbidity and mortality in Western countries. The prognosis is substantially worse than for chronic stable angina. The rate of in-hospital death and re-infarction is 5-10%. Despite optimal treatment with anti-ischaemic and antithrombotic drugs, death and recurrent MI occur in another 5-10% of patients in the month after an acute episode. Indian patients who have ACS have higher rate of STEMI than do patients from developed countries. Because most of these patients were poor, less likely to get proper treatments and have greater 30-day mortality. Patients with ACS in India tend to be young from low socioeconomic groups, and have higher rate of ST elevated MI than do patients of developed countries. Patients in India receive late medical attention and low access to proven therapies. Because of this poor patients have higher 30-day mortality.

Common risk factors attributed to ACS are hypertension, hyperlipidaemia, diabetes, smoking, tobacco use and family history of atherosclerotic disease.

2.1.2 Pathogenesis of ACS

The pathogenesis of ACS include disruption of atheromatous plaque which is further characterised by fissuring or rupture of these plaques – and consequent exposure of core constituents such as lipid, smooth muscle, and foam cells – leading to the local generation of thrombin and deposition of fibrin. This process stimulates platelet aggregation and adhesion resulting into the formation of intracoronary thrombus.

Unstable angina and non-ST elevation MI are generally associated with white, platelet rich, and only partially occlusive thrombus which can detach and embolise downstream, causing myocardial ischemia and infarction. In ST segment elevation (some time also referred to as Q wave) MI has red, fibrin-rich, and more stable occlusive thrombus.
2.1.3 Symptoms of ACS

Midline anterior discomfort due to angina most often at rest, severe new-onset or increasing in nature, which may last for at least 20 minutes is well known classical symptom of ACS. Discomfort in chest due to angina may radiate to shoulder, down the left arm, to the back, or to the jaw. Other secondary symptoms include nausea, vomiting, diaphoresis, or shortness of breath.

2.1.4 Diagnosis

UA and NSTMI are closely related conditions with clinical presentations that may be difficult to distinguish. Their distinction depends on whether the ischaemia is severe enough to cause myocardial damage and the release of detectable quantities of markers of myocyte necrosis. Cardiac troponin I and T are the preferred markers as they are more specific and reliable than creatine kinase or its isoenzyme creatine kinase MB.

**Fig. 2.1: Cardiac enzymes markers released after the onset of acute MI** (Anderson et al., 2013)

A 12 lead ECG is performed within 10 minutes of presentation to the emergency department or pre-hospital and checked for changes. An electrocardiogram may be normal or may show minor non-specific changes, ST segment depression, T wave inversion, bundle branch block, or transient ST segment elevation that resolves spontaneously or after nitrate is given. Physical examination may exclude important differential diagnoses such as pleuritis, pericarditis, or pneumothorax, as well as revealing evidence of ventricular failure and haemodynamic instability.
2.1.5 Management of ACS
Platelet aggregation and thrombus formation play an important role in ACS. The recent advances in pharmacotherapy such as glycoprotein IIb/IIIa inhibitors, LMWH, and clopidogrel have given new hopes to the healthcare providers. Further, safer and optimal use of percutaneous intervention has gained widespread acceptance.

As patients with unstable angina or NSTEMI represent a heterogeneous group with a wide spectrum of clinical outcomes, customising treatment to match risk not only ensures that patients who will benefit the most receive appropriate treatment, but also avoids potentially hazardous treatment in those with a good prognosis.

2.1.6 Medical Intervention
Medical treatment for ACS includes bed rest, oxygen, opioid analgesics to relieve pain, and anti-ischaemic and antithrombotic drugs. These are started at once on admission and continued in those with probable or confirmed unstable angina or NSTEMI. Anti-ischaemic drugs include intravenous, oral, or buccal nitroglycerin, beta blockers, and calcium antagonists. Antithrombotic drugs include aspirin, clopidogrel, intravenous UFH or LMWH, and glycoprotein IIb/IIIa inhibitors.

In case of STEMI the ruptured atheromatous plaque occluding epicardial coronary artery and further development of thrombus over it causes ischemia. The main aim of the medical intervention is to restore blood flow in the occluded artery. There are two methods for opening of occluded artery, first being administration of thrombolytic agents and the second is PCI.

Even though thrombolysis is the commonest form of treatment for STEMI it has some noticeable limitations such as a rate of revascularisation (restoring normal flow) in 90 minutes of only 55% with streptokinase or 60% with accelerated alteplase; a 5-15% risk of early or late reocclusion leading to acute MI, worsening ventricular function, or death; a 1-2% risk of intracranial haemorrhage, with 40% mortality; and 15-20% of patients with a contraindication to thrombolysis.

Primary PCI mechanically disrupts the occlusive thrombus and compresses the underlying stenosis, rapidly restoring blood flow. It offers a superior alternative to thrombolysis in the immediate treatment of STEMI.
2.1.7 Conservative and early invasive therapy for ACS

The conservative treatment usually involves intensive medical management, followed by risk stratification using non-invasive means (usually by stress testing) to identify the patients who may need coronary angiography. Early risk stratification will help identify high risk patients, who may require early treatment with glycoprotein IIb/IIIa inhibitors, angiography, and coronary revascularisation. Patients who may require invasive therapy (PCI) should receive a glycoprotein IIb/IIIa inhibitor and stenting as appropriate.

2.2 Humanistic Outcome Evaluations

The outcomes of the therapy have different perceptions among stakeholders. A physician who is the major provider of healthcare traditionally perceives on good clinical outcomes along with the focus on patients comforts and economy of treatment. On the contrary third party payers would perceive the social benefits with a rider on economic implications. Insurance companies may be overemphasising on cost containment and can engage focussed efforts on generic medicines as well as the cost saving approaches. The patients who are the primary sponsors of treatment, directly or indirectly has to consider equal importance on all three outcomes like clinical, economical and humanistic. The hierarchy of decision making lies with the physician at top and hence are decision makers who also make the patient to agree to their decision to be the finally accepted decision. In due course due to change in the socio-cultural scenario empowering the patient with knowledge started participating in clinical decision making. The awareness and access of knowledge with an improved communication facilities the patients are able to understand the technicalities of treatments and are questioning the value of treatment in perception of cost and risks involved.

The definition of health as given by world health organisation (WHO), health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity (Missoni and Committee, 2006). The conventional approach of health was changed as it was observed for sustenance of health socio-economic factors have a profound impact on health. The measurement of health was extended form clinical outcomes to quality of life and economic containment. There was a need to invent tools for measurement of quality of life along with the treatment and cost comparisons. This has led to development of new faculty under the nomenclature of pharmacoeconomics and outcomes research. Pharmacoeconomic evaluations range from different stake holder perceptions along with highlighting the effectiveness of alternative treatments.
The quality of life, a purely subjective matter was difficult to measure and analyse. The inventions and research approaches has made this qualitative data into quantitative data suitable for statistical evaluations leading to highly reliable humanistic outcomes databases. There was a need to link the humanistic outcomes with pharmacoeconomic data as this would make the impact of the variables of clinical, economical and humanistic outcomes on a common platform summarising overall efficacy of the product or service, for example QALY, quality adjusted life expectancy (QALE), disability adjusted life years (DALY) etc.

The humanistic outcomes are measured by validated set of questionnaire, which are classified as generic and disease specific. Generic questionnaires are those which focus on extracting the overall quality of life experienced by the patient during treatment period (Smith MD et al., 2003). Whereas the disease specific instruments focus on special aspects of disease which are disease conditions. For example EQ-5D measure the overall quality of life where as MacNew questionnaire covers the morbidity impact of angina patients. The questionnaires are usually measured on the Likert scale of five with central tendency and exceptions of measurement based on requirement. The questionnaires need to be translated and scrutinised for cultural compatibility by running trial pilot studies. Finally the measurements data is subjected to vigorous statistical analysis and sensitivity tests to get a clear picture of validity of measurements.

The instruments of quality of life measurement should aim at quantifying specific morbidity the patients are likely to face during the disease and treatment. The patients who is under treatment for MI has his own disabilities along with physical deficiencies, which might also has been compounded as psychological illness as depression and feeling lonely. It is very important to put these intricate points into the grid of questionnaires as this would bring out the level of patient satisfaction or dissatisfaction for a particular treatment or service he is undergoing. Hence, the questionnaires especially the disease specific focus on the morbidity and mortality of particular disease and prognosis of recovery of disease. This would help to get a detailed data regarding the patient’s expression of satisfaction or dissatisfaction. The questionnaires are usually prepared for a particular society or community. Cultural compatibility for adaptation of instruments into actual study needs careful approach and shall proceed with caution.

The nature of measurements in quality of life studies are usually qualitative. However, qualitative data is not suitable to adopt and analyse in any robust statistical methods of
analysis. The statistical analysis is mandatory for an instrument to be accepted for its reliability and reproducibility. As a result of this the quality of life measurements which are called psychometric tools focus on conversion of the qualitative data into a numerical quantitative data. The ranking of the expression of patients regarding ability to do, extent of happiness, severity of the pain are recorded on a ranking scale. Further these values are summed up as domain scale or summary scores, which are either statistically compared or evaluated as a preference choice.

2.2.1 Role of HRQoL instruments in pharmacoeconomic evaluations

Physicians and other healthcare providers are compelled to balance risks and benefits of any treatment due to scarcity of resources. The benefits, with chosen treatment option must justify the resources spent on it. Usually in a developing countries like India where the resources of many families are limited they have to forgo other benefit to avail healthcare provision, and hence, informed decision making becomes very important. To understand the benefit gained or the perceived value of any treatment option, health related quality of life instruments are used which also aid in economic evaluations.

2.2.2 Health status and its Measurement

The health status is as complex as the definition of health itself due to the multidimensional nature of the health status. The factors which are very important to assess the status of health include social, physical and psychological dimensions. Further each dimension has a distinct aspects. For example the physical status has a dimension of self-care and the pain perceived. Similarly, social domain has daily activities and also day to day basic life skills like grooming, and dressing up. The psychological domain comprises of perceived anxiety and also the depression due to illness. All these parameters are of qualitative in nature and difficult to quantify. Further, when one want to correlate economic value of each of these domains, it becomes extremely difficult. The question is how we should find what is the value of anxiety, pain and discomfort in terms of monetary value? Again complexity is added as the particular patient’s daily income varies depending upon their earning capacities. Taking into consideration, above discussed nature of health status an its impact on individual earning capacities, there is a need to invent and adopt simple, acceptable, dependable instruments of health status measurements. Lis of commonly used HRQoL instruments is given in Table 3.1
### Table 2.1: List of commonly used HRQoL instruments

<table>
<thead>
<tr>
<th>Sl No</th>
<th>Full Name</th>
<th>Abbreviated Name</th>
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<tbody>
<tr>
<td>1</td>
<td>15-dimensional health-related quality of life measure (Sintonen, 2001)</td>
<td>15D</td>
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<tr>
<td>2</td>
<td>Brief Hospice Inventory (Guo et al., 2001)</td>
<td>BHI</td>
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<tr>
<td>3</td>
<td>Centres for Disease Control and Prevention Health-Related Quality of Life Measure (Control)</td>
<td>CDC HRQOL-14</td>
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<tr>
<td>4</td>
<td>Client Satisfaction Questionnaire (Attkisson and Greenfield, 1999)</td>
<td>CSQ</td>
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<tr>
<td>5</td>
<td>Duke Health Profile (Parkerson Jr et al., 1990)</td>
<td>DUKE</td>
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<tr>
<td>6</td>
<td>Duke Severity of Illness Checklist (Parkerson et al., 1993)</td>
<td>DUSOI</td>
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<tr>
<td>7</td>
<td>Euroqol EQ-5D (de Charro)</td>
<td>EQ-5D</td>
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<tr>
<td>8</td>
<td>Functional Status Questionnaire (Jette et al., 1986)</td>
<td>FSQ</td>
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<tr>
<td>9</td>
<td>Glasgow Health Status Questionnaires (Gatehouse et al., 1998)</td>
<td>GHSQ</td>
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<tr>
<td>10</td>
<td>Health Assessment Questionnaire (Fries et al., 1982)</td>
<td>HAQ</td>
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<tr>
<td>11</td>
<td>Instrumental Activities of Daily Living (Lawton and BRODY, 1970)</td>
<td>IADL</td>
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<tr>
<td>12</td>
<td>Nottingham Health Profile (Hunt et al., 1981)</td>
<td>NHP</td>
</tr>
<tr>
<td>13</td>
<td>Quality of Well Being scale (Kaplan et al., 1984)</td>
<td>QWB</td>
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<tr>
<td>14</td>
<td>Satisfaction profile (Bertaccini et al., 2004)</td>
<td>SAT-P</td>
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<tr>
<td>15</td>
<td>WHO (Five) Well-Being Index (Heun et al., 2001)</td>
<td>WHO-5</td>
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<tr>
<td>16</td>
<td>World Health Organization Quality of Life assessment instrument (group, 1995)</td>
<td>WHOQOL L-100 &amp; WHOQOL L-BREF</td>
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<tr>
<td>17</td>
<td>Health Status Questionnaire 2.0 (Radosevich et al., 1994)</td>
<td>HSQ</td>
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<tr>
<td>18</td>
<td>Health Utilities Index (Horsman et al., 2003)</td>
<td>HUI</td>
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<tr>
<td>19</td>
<td>McMaster Health Index Questionnaire (Chambers, 1993)</td>
<td>MHIQ</td>
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<tr>
<td>20</td>
<td>Quality of Life Index (Ferrans and Powers, 1985)</td>
<td>QOLI</td>
</tr>
<tr>
<td>21</td>
<td>Short Form 36 (Ware et al., 2000)</td>
<td>SF36</td>
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Patient preferences for alternative health states can be measured either by Time Trade-Off (TTO) method or Standard Gamble Method. The TTO measure values whereas Standard Gamble method measures utilities.

**2.2.2.1 Time Trade-off Method:**

In Time Trade-Off (Torrance et al., 1972) patients are asked to imagine living their life in present state and to contrast alternative life in perfect health for exchange of shorter life period. Patients are posed with alternative years of life in present status against the years of life in perfect health state.
For example, if an individual with 30 years of life with hip fracture due to osteoarthritis, is ready to trade off 15 years to achieve rest of 15 years in perfect full health, the QALYs of 1 year with hip fracture due to arthritis would be 0.5.

2.2.2.2 Standard Gamble Method:

Standard Gamble method (Von Neumann and Morgenstern, 2007) measures utility and is based on the Utility Theory, first proposed by Neumann and Morgenstern. The Utility Theory describes how a rational individual makes decisions when facing uncertainty. Here, patients are asked to imagine about an intervention that would result into perfect health but with associated risk of death. Further, patients are asked to indicate the highest probability of death risk they are willing to accept against choosing to remain in their present health condition. If the perceived value of the current health condition is low, patient is ready to accept larger probability of death risk. Patients are asked to place the utility of present health between death (value 0) and full health (value 1).

For example, if a woman suffering from breast cancer is impassive between her current health state and is willing to gamble when the probability of dying is 50%. This would mean that the utility the individual places on a year in that health state is 0.5, against a year in perfect health, which would be 1.0.

Visual Analogue Scale (VAS) is another commonly used value based measure. VAS allows patients to rate their health status from 0 meaning worst to 100 meaning best (Schünemann et al., 2003).

2.2.2.3 Selection of HRQoL Instruments

Preference and perception measuring for health states, by either Standard Gamble or TTO can be time consuming and complex. Hence recently developed pre-scored multi-attribute health status classification system is gaining more popularity among researchers. In these instruments, patients were asked to rate their ability to function in physical, emotional, and social aspects of life. The patients report their health state rather than their preference for different health states. Some commonly used instruments under this category are European Quality of Life Scale (EQ-5D), Short Form 36 (SF-36), Short Form 6D (SF 6D), Health Utilities Index (HUI) and Well-Being Scale.
To provide an assessment of patients’ HRQoL, researchers can either select tools that focus on general health status using generic instruments, or they can choose instruments that focus on specific aspects of disease under study using disease-specific measures. The choice of correct HRQoL instrument depends on the objectives of the researcher or decision maker, which may be to record treatment outcome, differentiate between patients with different disease severity and to record change in quality of life over a period of treatment.

Once the objectives of assessments are made clear, researchers should look into various aspects such as whether the instrument required is disease specific or generic. Various steps involved in the selection process of HRQoL instruments are shown in Fig. 1.

A disease-specific measure is designed to understand specific aspects of health that are affected by the disease of interest (deep vein thrombosis). In contrast, a generic instrument measures general health status, including physical symptoms, function and emotional dimensions of health relevant to all health states, including healthy individuals (Jackowski and Guyatt, 2003).

Disease-specific instruments are more responsive to small but important changes in health states than are generic measures (Jackowski and Guyatt, 2003). Because the items on a disease-specific HRQoL instrument are so focused on a particular disease, conversely, they cannot be used to compare the impact of one disease with another. In some cases, disease-specific measures are so specific that comparisons between different populations with the same disease conditions are not possible (e.g., paediatric versus adult populations in asthma). The generic HRQoL instruments are useful when measuring the impact of a specific illness or injury across different diseases, severities, and interventions. For a comprehensive picture of a patient’s HRQoL, it is often desirable to include a combination of both, the generic health and disease-specific instruments.

The examples of disease specific include adult and diabetes dependent quality of life questionnaire, Seattle angina questionnaire, Minnesota living with heart failure, angina pectoris quality of life questionnaire etc.,
The desirable instrument should be having the proof of

- A. Reliability (consistency in ratings),
- B. Validity (representation of theoretical constructs) and
- C. Responsiveness (detect even small changes)

A. Reliability:

Reliability quests the consistency of the instrument, does the instrument produce same score on repeated administrations? Thus confirming the extent to which the instrument is devoid of error. Reliability quests the discrimination power of the instrument between individuals in a given population consistently when respondents are in stable health. Reliability will appear greater when measured in a heterogeneous group with higher variability in scores between patients (includes patients with no pain to those with severe pain) than in a homogeneous group of patients.

There are three types of reliability measurements, they are
a) Test-retest reliability
b) Internal consistency reliability
c) Inter-rater reliability

a) Test-retest reliability (Rascati, 2013) evaluates the similarity between health status scores over time when no changes in health have occurred. That means if the same person completes HRQoL instrument and then retakes the same survey after some period, if the person's health status has not changed, his or her scores from both attempts should be similar or consistent. It is normally determined using Cohen's Kappa or Pearson's or Spearman's correlation coefficient. Normally, levels in excess of 0.6 indicate adequate test-retest reliability.

b) Internal consistency is an estimate of homogeneity of items measuring a specific health domain and is normally measured using Cronbach's alpha. The closer the coefficient is to 1, the greater the homogeneity between the items and, therefore, the greater the confidence. For example consider asking two questions from vitality domain of SF-36 HRQoL instrument to the person, did you feel full of pep? and did you have a lot of energy? The questions should produce similar answers from the person. Internal consistency measure has limitations as it relates only to the correlation between items on a single administration, and does not assess the extent of variability on repeated administration of a measure.

c) Inter-rater reliability assesses the agreement between different scores collected by administering the same instrument in a group of healthy people.

It should be noted that if an instrument is tested and found to be reliable yet not precise (invalid), means the instrument can be reliably incorrect. If the instrument in question consistently produces incorrect answers, it is reliable but not valid.

B. Validity:

Validity (Arnold, 2009) measurements are essential to confirm that the scores produced by the instrument truly represent the basic constructs of HRQoL instrument. In other words, validity assessment of an instrument evaluates whether instrument in question measures what is intended. The assessment of validity of an instrument is easy than the reliability.

There are three types of validity measurements, they are
a. Content validity

b. Construct validity

c. Criterion validity

a. Content validity evaluates whether the HRQoL instrument contain all facets of relevant variable of interest. Content validation requires standard variables against which the instrument in question needs to be validated. These standard variables can be based upon well accepted theoretical definitions of constructs, on existing accepted standards or from the experiences of patients affected, health-care providers or decision makers. Face validity explains whether the contents look complete and valid to the examiners who take it, the administrative personnel who decide on its use, and patients. Content validity always require more stricter statistical tests than face validity, which only requires an intuitive judgement by the examiner.

b. Construct validity measures the extent to which the instrument in question actually relates itself to different measures of constructs it should theoretically. Two basic type of construct validity are convergent and discriminant validity. Convergent validity measures extents to which the interpretations of scores are similar to the interpretations of another instrument measuring similar constructs theoretically.

c. Criterion validity evaluates that HRQoL scores are explicitly related to one or more external outcome criteria. For example higher HRQoL scores indicate pharmaceutical therapy adherence hence low morbidity and lower HRQoL scores may correlate to non-adherence to pharmaceutical therapy hence high morbidity.

When sufficient evidence is collected to indicate that an instrument reveals the health concepts, one can conclude that the HRQoL instrument is validated. It also mean that the process of validation continues till new meaning and interpretation is given to instrument scores.

C. Responsiveness:

Responsiveness of an instrument used to measure HRQoL is the ability of that instrument to identify or detect changes in the health status of a given group of patients. Sometimes sensitivity to change and responsiveness are used interchangeably, but there are some important differences. Sensitivity to change refers to the ability of an instrument to measure
true change in the health state being measured regardless of whether it is relevant or meaningful to the patient or researcher. In contrast, responsiveness refers to the ability of the HRQoL instrument to detect changes which are important to the patient in the health state being measured even if that difference is small (Kirshner and Guyatt, 1985).

Interrelated with the measurement of responsiveness the quest what change in score is clinical difference, which is often referred as minimally important difference (MID). Hence MID refers to the smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important and that would lead the patient or researcher to consider a change as relevant (Schünemann and Guyatt, 2005).

2.2.3 EQ-5D-5L

EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (Group, 1990). Applicable to a wide range of health conditions and treatments, it provides a simple descriptive profile and a single index value for health status that can be used in clinical and economic evaluation of healthcare as well as in population health surveys (Rabin and Charro, 2001).

The EQ-5D-5L consists of 2 pages – the EQ-5D-5L descriptive system and the EQ visual Analogue scale (EQ VAS). It has 5 dimensions - mobility, self-care, usual activities, pain, and anxiety. However, each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The respondents are asked to indicate their health state by ticking in the box against the most appropriate statement in each of the 5 dimensions. The combined 5 digit number describes the respondent’s health state and it should not be used as a cardinal score (Herdman et al., 2011).

A total of 3125 possible health states are defined in this way. Each state is referred to in terms of a 5 digit code. For example, state 11111 indicates no problems on any of the 5 dimensions, while state 12345 indicates no problems with mobility, slight problems with washing or dressing, moderate problems with doing usual activities, severe pain or discomfort and extreme anxiety or depression.

The EQ VAS records the respondent’s self-rated health on a 20 cm vertical, visual analogue scale which enables the respondents to place their current health state on a range from 0
(worst imaginable health state) to 100 (best imaginable health state). It can be used as a quantitative measure of health as judged by the individual respondents (Brooks and Group, 1996).

EQ-5D 5L is designed for self-completion by respondents and is cognitively undemanding, taking only a few minutes to complete. EQ-5D-5L health states, may be converted into a single index value. The index values, presented in country specific value sets, are a major feature of the EQ-5D 5L instrument, facilitating the calculation of quality-adjusted life years (QALYs).

2.2.3.1 Validity and Reliability of EQ-5D questionnaire

In a study, 106 consecutive patients with ACS completed the EQ-5D, the SF-36, and the MacNew questionnaire at admission, at discharge, and at three months of follow up. Validity, reliability, responsiveness, and acceptance of the EQ-5D were tested. The results demonstrated that EQ-5D was highly accepted. The EQ-5D index showed substantial ceiling effects after rehabilitation. The EQ-5D visual analogue scale (VAS) score and EQ-5D index were significantly better for patients with MI than for patients who underwent surgery (both \( p < 0.001 \)). The correlation with the MacNew sub scores and with the global score was significant. Hence, it was concluded that the EQ-5D has all qualities to be used in ACS (Schweikert et al., 2006).

In a study aimed to quantify the relationships between the EQ-5D index and commonly used cardiac measures, Canadian Cardiovascular Society (CCS) angina severity class, treadmill exercise time (TET) and Seattle Angina Questionnaire (SAQ) were examined. This study concluded that EQ-5D index value decreases as severity of cardiac disease increases (Goldsmith et al., 2009).

In another study carried out to confirm the contributions of different disease related, pathway related and demographic variables on patients’ perceived HRQoL as a relevant and widely used outcome measure in cardiac populations using EQ-5D (Kramer et al., 2012).

2.2.4 Effect of PCI on HRQoL

According to TRIUMPH registry, the registry of acute MI patients of United States, 4340 patients were subjected to detailed interview, and quality of life was assessed by Seattle Angina Questionnaire (disease specific) and EQ 5D and SF-12 (generic) questionnaires.
Patient’s baseline independence was assessed by EQ 5D, 72.9% in which respondents had no problems with mobility, 90.3% had no problems with self-care and 66% had no problems with usual activities. Over the follow up period of one year, 43% experienced either independence or physical function decline. On subgroup analysis, decline in mobility (58.2%) and usual activities (65.5%) were more common than in self-care group (21.4%). In patients with an improvement in angina, when compared to baseline- 21% experienced decline in physical function (Dodson et al., 2012).

Benzer et al, conducted a study to describe the impact of PCI, CABG or continued medical treatment on quality of life for the patients of CAD. MacNew questionnaire was used in the project. The association between MacNew scale at baseline and angina grade was significant along with moderate correlation for global, physical, emotional and social subscales. Mean Baseline scores for PCI ware, 4.9, 5.1, 5.3, and 5.0 for physical, emotional, social and global score respectively. After a follow up period of one year, mean change (95% Confidence Interval) for PCI ware, 0.8, 0.52, 0.59, 0.58 for physical, emotional, social and global scores respectively. Global, Social and emotional scale significantly improved for PCI group of patients where as emotional and global scale improved in CABG group. Improvement in angina grade and each MacNew scale were moderately correlated (Benzer et al., 2003).

Research group of Stent – PAMI trial, published the quality of life for the patients undergoing PCI or balloon angioplasty for the patients of acute MI. Research team used the SAQ and SF – 36 questionnaires to assess quality of life. At one month of follow up, PCI group had reported less bodily pain (76.3 to 80.8) than balloon angioplasty patients and at six months, PCI resulted in significant reduction in angina frequency 89.3 to (94.3) and bodily pain (76.3 to 78.9) and improved disease perception. At 12 months follow up, differences were not significant. These results favoured the initial stenting being beneficial for the acute MI patients (Rinfret et al., 2001).

Research group of RITA – 3, published an article on HRQoL after Interventional or conservation strategy with unstable angina or NSTEMI patients. Patients from England and Scotland who experienced the UA or NSTEMI were randomized into Intervention strategy including PCI and conservation strategy involving pharmacotherapy. HRQoL was assessed using EQ 5D and EQ VAS, SF-36, and SAQ questionnaires. Four months and one year follow up was conducted. The improvement in the intervention group at 4 months was significant (mean difference of 3.0). Results at one year showed, increase in mean VAS score favouring
Intervention group. Larger percentage of patients in Conservation group had worsening HRQoL with respect to, usual daily activities and anxiety. Global utility scores at one year were significantly better for the intervention group. SAQ domains were significantly better in all the domains for the intervention group, specifically with disease perception (Kim et al., 2005).

In a cross sectional study conducted in Australia, 202 patients who underwent PCI procedure answered MacNew questionnaire after one year of the index PCI. Mean emotional score of 5.24 ± 1.2 along with mean physical score of 5.05 ± 1.3, mean social score of 5.43 ± 1.4 along with mean global score of 5.17 ± 1.2 were recorded. However, the trends of decline in the values were seen after 24 months in all domains. Overall HRQoL scores for all domains increased in patients at 15 to 17 months after index PCI was observed (Fernandez et al., 2007).

Daniel Mark et al., for the Occluded Artery Trail, compared PCI with Medical therapy alone in totally occluded infarct related MI. They assessed quality of life in 951 patients by Duke Activity Status Index (DASI) and SF – 36 at baseline, 4, 12 and 24 months. The mean difference between groups in the DASI score was 1.00 (p=0.36) at 12 months and 1.7 (p=0.29) at 24 months, with higher scores at PCI group. The difference in the percentages of patients reporting angina at 24 months was smaller for PCI group (11.9% in therapy and 7.1% in PCI. P=0.03). In Score on Mental Health Inventory, the mean difference of 1.8 was observed in PCI group at 24 months (Mark et al., 2009).

The PCI patients treated with DES were asked to participate in quality of life measurement study done at Netherlands. EQ 5D and EQ VAS were used as tool for assessment. EQ 5D levels were dichotomized into no problems and problems; VAS was dichotomized using the 25th percentile (Cut off ≤ 60) indicating poor health status. Mobility (HR: 2.23), self-care (HR: 3.09) and low health status (HR: 3.09) as per VAS were independent predictors of death (Pedersen et al., 2011).

In Austria, researchers tried to observe the changes in HRQoL and mental distress after PCI procedure. MacNew and hospital anxiety and depression scale questionnaires were used at 1, 6, 12 and 24 months. Improvement of MacNew scale was found up to 6 month after PCI. Mental distress declined during the first month of the follow up period. MacNew global score increased significantly as improvement in all three subscales were improved at 1 month and
6 months. After 6 months up to the end of 24 months, scores remained stable (Sipötz et al., 2013).

In a study conducted in Sweden, HRQoL was determined in the PCI patients using SF-36 and HADS questionnaires. An improvement in HRQoL at 1 year was noted for both men and women, when compared to 5 months follow up after MI. Women reported scores on mental health (p<0.01) and men in physical health domain (Brink et al., 2005).

In a study carried out in Norway, the researchers were concluded that, the largest improvements were seen in scores related to physical functioning of SF-36 (mean overall change from baseline to follow-up was 6.9 points, p < 0.001) and lowest in the mental health domains (p<0.001) (Melberg et al., 2010).

Study done by Kahler et al., shows the improvement in the quality of life in both octogenarians and age group of 60-70, significantly in the physical abilities and decrease pain (Melberg et al., 2010).

In a study, assessing the dimension-specific burden of disease among cardiovascular diseases, problems with usual activities seem to be most common, followed by problems with mobility and pain (Dyer et al., 2010).

Most of the researchers compared both CABG and PCI group of patients for HRQoL measurements. Hofer and colleagues reported that, the short and intermediate-term results revealed HRQoL differences between PCI and CABG in the month immediately after intervention despite almost identical reduction in angina severity over the first month in both groups. PCI was associated with a relatively rapid increase in HRQoL in the first month, with little further change by 3 months (Höfer et al., 2006).

Zhang et al reported that, both CABG and stent-assisted PCI resulted in significant improvement in angina-related health status at 6 months and 1 year after intervention (Zhang et al., 2003).

Significant difference arises from better physical function for CABG patients than PCI patients. But, the mental health status remained similar in both the groups (Szygula-Jurkiewicz et al., 2005). HRQoL in both patients group was increased statistically significant by 6 months. No significant change in health-related quality of life took place in either group from 6 to 12 months (Kattainen et al., 2006).
In a multicentre study, patients with UA/NSTEMI and STEMI underwent PCI, along with evaluation of HRQoL. After PCI, both angina specific and general HRQOL scores were improved, but improvement was much more frequent in angina-related HRQOL of patients with UA/NSTEMI than those with STEMI (44.2% v/s 36.8%, P < 0.001). At 30-days after PCI, angina-specific HRQOL of the patients with UA/NSTEMI was comparable to those with STEMI (P = 0.521), but general HRQOL was significantly lower after adjusting baseline characteristics (P < 0.001). The general health status of those with UA/NSTEMI was not good even after optimal PCI (Kim et al., 2013).

2.3 Pharmacoeconomic Evaluations

Pharmacoeconomics is the scientific discipline, which evaluates the clinical, humanistic and economic aspects of pharmaceutical products, services and programs to provide healthcare decision makers, providers and patients with valuable information for optimal outcomes and allocation of healthcare resources. Pharmacoeconomics is branch of health economics which particularly focuses on costs and benefits of a drug therapy (Bootman et al., 1996).

Knowledge of pharmacoeconomics is therefore, very important for clinical and practicing pharmacists who are involved in promoting rational prescribing. In some countries like Australia, evaluations are officially required before the drug is approved for the reimbursements, even though the drug has proven safety, efficacy and tolerability which make economic evidence as “fourth hurdle”. The Pharmaceutical companies are considering economic evaluations along with clinical trials as a necessity to effectively market their drugs (Muragundi, 2014).

Pharmacoeconomic studies involve both costs and outcomes. The input is the cost component of healthcare provision and the output is the benefit or outcomes measured. In between the cost and the benefit there may be any product, service or program. If we measure only one side of it the evaluation is incomplete. Hence it is very important to measure and compare both costs and benefits (Mason, 1997).

2.3.1 Cost Measurements

All pharmacoeconomic evaluations have a common structure of measurement of costs and outcomes as discussed above. The costs involved in a drug therapy may not only include price paid for drug and its use but it actually involves all associated consequences of the drug
therapy including time lost for work and distress. For the purpose of pharmacoeconomic evaluation costs can be categorized into four types (Jolicoeur et al., 1992).

a. Direct Medical Costs
b. Indirect Medical Costs
c. Indirect Costs
d. Intangible costs

a. Direct medical costs: These are most obvious and easy to identify and measure. All the inputs involved in providing a drug treatment are direct medical costs. The examples include cost of drugs, medication monitoring, administration of drug, diagnostic tests, hospitalization costs, out-patient costs, nursing services etc.
b. Indirect medical costs: These are the costs which are not associated with drug therapy but are incurred by the patients and their families and are nonmedical in nature. Examples are; travel costs to receive treatment, cost of food while traveling out of town to receive treatment, hotel stay for patient and patient attendants.
c. Indirect costs: Indirect costs involve the costs that results from the loss of productivity earnings or leisure time because of illness and death. Indirect costs are experienced by patients, family members, friends, as well as society.
d. Intangible costs: These include the costs of pain, suffering, anxiety or fatigue that occur because of illness or the treatment of illness which a patient and his family members may suffer. These are difficult to measure in monetary terms but are of importance to both patients and physicians. HRQoL is an important measurement which helps in integrating intangible costs into a pharmacoeconomic analysis.

2.3.2 Outcome Measurements

The outcomes or benefit measurement need to be equally comprehensive by including all impacts on the patient’s life because of drug therapy. There are three types of benefits which are measured for pharmacoeconomic evaluation (Freund and Dittus, 1992)

a. Natural Units
b. Utility Units
c. Associated economic benefits
a. Natural units: This the direct measure of drug therapy. For example; reduction in blood pressure, reduction in HbA1c, strokes prevented, and ulcers healed etc.

b. Utility units: When a patient undergoes drug therapy he/she moves from one health state to another resulting in changes in satisfaction or sense of well-being, which is measured in terms of utility units. These measurements are based on measurement of ‘quality of life’. Quality of life measure includes measurement of physical, social and emotional impact of illness as well as change occurred due to drug therapy. Physical measures focus on presence or absence of pain or immobility whereas psycho-social dimension focus on level of anxiety and depression experienced, and also the ability of the patient to cope with problems. While the output of such measurement may be given in terms of ‘health profiles’, which keeps all the aspects of measurements separate or it may also be given in terms single summery measure ‘quality adjusted life years’ (QALY). QALY is a single summery measure which measures both quality and quantity of life.

c. Associated economic benefits: are the measurements of all the benefits in terms of monetary units (i.e., Rupees) because this is the useful common denominator to compare treatments of two deferent diseases. This concept includes, for example the economic burden or benefit that a society incur as consequence of patient’s health improvement resulting in returning to work.

2.3.3 Echo Model

The ECHO model stands for Economic, Clinical and Humanistic outcomes model, which was formulated in order to find the relationship between all the three important areas of healthcare. The economic component refers to cost and resource utilization. The clinical components refer to clinical measures such as mortality, cure rates and laboratory value goals. The humanistic components refer to patient reported, quality of life and QALY measures. This is the most comprehensive economic evaluation model which encompasses all aspects of drug therapy impact to help in decision making (Kumar and Baldi).

2.3.4 Perspective of Pharmacoeconomic Evaluation

Pharmacoeconomic analysis should always state the perspective of their study because this perspective will determine the costs need to be identified and measured. There are four generally accepted perspectives (Rascati, 2013).
a. **Payer Perspective**: Payers for the healthcare can be government, insurance companies and it can also be employers. This includes all the direct medical costs involved in the treatment of an illness as payers are the ones responsible for choosing right policy, therapy or the formularies.

b. **Provider Perspective**: Providers of healthcare can be hospitals, individual physicians or managed care organizations. This perspective considers the cost of providing the healthcare or drug therapy rather than billed cost.

c. **Patient Perspective**: This aspect considers the cost incurred to the patient when patients choose to take treatment or drug therapy. This perspective includes direct medical cost to patients and also includes indirect costs like time lost from work and travel costs. This is the most important perspective in Indian context because majority of the costs for healthcare are met by out of the pocket spending by the patients or their family.

d. **Societal Perspective**: This is broadest of all the perspective, which incorporates all the costs and benefits to society as a whole. Commonly all direct and indirect costs are considered for pharmacoeconomic evaluations involving societal perspective.