Nigerian Journal of Pharmaceutical and Biomedical Research
Vol. 6 Issue.1 April, 2022. p-ISSN: 2579-1419 e-ISSN: 2814-1423

Cost-effectiveness analysis of combined antidiabetic therapy for type 2 diabetes mellitus in a tertiary health institution in north-central Nigeria

Giwa H. Bukola[1], Abdulganiyu Giwa[1], Jamiu O. Muslim [1], Sanni Nasiru[2], Saadu R. Ajibola[1,3], Abolarin Busayomi[1,4]

[1] Department of Clinical Pharmacy and Pharmacy Practice University Of Ilorin Ilorin, Kwara State, Nigeria

[2]Diabetes Clinic, Department of Medicine, University of Ilorin Teaching Hospital Ilorin, Kwara State, Nigeria

[3]Pharmacists Council of Nigeria, Kwara State Field Office, Ilorin, Kwara State, Nigeria

[4] Pharmacy Department, University of Ilorin Teaching Hospital Ilorin, Kwara State, Nigeria

Abstract

Background: *Anti-diabetic therapy is a lifetime treatment for patients suffering from diabetes mellitus. This translates into a substantial cost in drug therapy to patients who pay out of pocket, most especially in developing counties.As a result, it will be beneficial to identify competing options in drug therapy in order to redirect resources with the aim of achieving more in terms of cost-effectiveness.*

Objective: *to assess the cost-effectiveness of combined antidiabetic regimens in patients with type 2 diabetes mellitus (T2DM) in University of Ilorin, Teaching Hospital, Ilorin, Kwara state, North- central Nigeria.*

Method: *A sample size of 276 casenotes from the total population was obtained after addition of a 5% attrition rate. A drug utilization study was then conducted through a one year retrospective review (January 2021 to December 2021) of the276 case notesThe casenotes were selected by systematic random sampling using sampling interval of 5. This was accompanied by using the World Health Organization-defined daily dose method of evaluating drug use. TheEuroQoltool (EQ5D) was employed to evaluate the effectiveness of the identified treatment options in terms of quality adjusted life years (QALYs).*

Results: *Combinations of Metformin/Glimepiride, Metformin/Linagliptin, and Metformin/Pioglitazone were identified anti-diabetic therapy options, with utilization patterns of 64.49%, 18.84%, and 16.67 %, respectively, and effectiveness of 0.755, 0.793, and 0.819 QALYs.*
Metformin/Linagliptin compared with Metformin/Glimepiride caused an incremental cost-effectiveness ratio (ICER) of 823.16 USD/QALYs which is < GDP/capita of Nigeria ($2, 097). Showing that Metformin/Linagliptin was more cost-effective.

Metformin/ Pioglitazone was dominant when compared with Metformin/Glimepiride, giving an ICER of -25.78 USD/QALYs, also showing that Metformin/ Pioglitazone was more cost effective. All ICERs achieved were robust to input parameter variation on sensitivity analysis.

Conclusion: *Combinations of Metformin/Linagliptin and Metformin/Pioglitazone were both found to be more cost effective than Metformin/Glimepiride in the management of type 2 diabetes.*

Keywords: Antidiabetics, Cost-effectiveness, Diabetes mellitus, Nigeria.

Introduction

Healthcare spending is on the increase in government, donors, private and societal perspectives. As such, judicious allocation of resources to the health sector is getting more and more pertinent (Kennedy et al 2009). The impact of cost containment is causing administrators and policymakers in the pharmaceutical sector to examine closely the cost and consequence of both proposed and existing interventions (Kesselheim et al 2006). Private and donor agencies are demanding that health problems be evaluated in terms of clinical, economic and humanistic outcomes(Gauvreau et al 2012).

Pharmaco-economic approach can be used to analyze the value of health services to the public, as opposed to the traditional market place scenario where values are measured by the prices that the patient or patron is willing to pay. The use of valid economic evaluation methods to measure the value and impact of new services can increase acceptance of such programs by the medical profession, third party payers and consumers (Ray 1979, Mc Ghan W 1993).

Moreover, with the depressing nature of economy in many countries such as Nigeria, where per capita income is low, there is need for utmost consideration for cost containment measures. The healthcare environment is clearly in a state of rapid evolution. Traditional approach to health care decisions will no longer suffice; therefore, new tools would be required. Medical, ethical and societal concerns about costs, access and quality of care are making healthcare practitioners to consider more comprehensive model for medical decisions (Bootman et al 1996, Scaria et al 2015) Consequently, interest in research to assess outcomes of healthcare has been increasing. These trends have led to the evolution of pharmaco-economics (Bootman et al 1996,Scaria et al 2015)Pharmaco-economics has been defined as the description and analysis of cost of drug therapy to health care system and society (Bootman et al 1996, Scaria et al 2015). It is a specialized aspect of health economics which involves the use of economic principles and techniques of analysis to ensure that scarce healthcare resources are used more efficiently. The objective of pharmaco-economic study is to influence policy formulation and effect decision making. This involves making a person or a group of people change their behaviour and persuade them that a new course of action is a "better" one. In economic terms, "better" simple means more efficient (Bootman et al 1996, Scaria et al 2015).

A cost-effectiveness analysis (CEA) measures costs in dollars and outcomes in natural health units that indicate an improvement in health such as cures, lives saved, or blood pressure reductions. This is the most common type of pharmacoeconomic analysis found in the pharmacy literature. An advantage of using a CEA is that health units are common outcomes that are routinely measured in clinical trials, so they are familiar to practitioners (Kennedy et al 2009).

Some researchers consider cost-utility analysis (CUA) to be a special sub-set of CEA that uses units such as quality-adjusted life years (QALYs) to collapse different types of outcomes into one unit of measure quality adjusted life years (QALY), use time and multiply number of years lived by the "quality" of those years. The process of adjustment of the years of healthy life lived is called "quality adjustment" (expressed as QALYs), and the process of adjustment of the years of healthy life lost is called "disability adjustment" (Expressed as DALYs) (Kesselheim et al 2006).

Diabetes mellitus is a chronic, debilitating and an expensive to manage condition which is caused by chronic hyperglycemia. Hyperglycemia causes harm to nearly all cell types in the body. Diabetes is linked to major consequences, puts families at risk, and makes it difficult to meet internationally agreed development goals, such as the Millennium Development Goals (MDGs) (Wertheimer 2014). Today, there are 537 million people living with diabetes. According to the World Health Organization, the number of individuals living with diabetes worldwide increased from 108 million in 1980 to 422 million in 2014, with obesity and overweight being the key risk factors (Scaria et al 2015).

Diabetes mellitus is widely known to be linked to an increased risk of morbidity and mortality. However, it is still unknown how this disease affects one's functional health status and sense of well-being (Scaria et al 2015). Several studies have shown that diabetes has a significant detrimental influence on HRQoL, particularly when complications are present (Walker et al 2012). Complications and comorbidities can have a significant impact on a patient's ability to manage their own care, affecting therapy adherence and efficacy. Such complications and comorbidities can have a significant impact on patients' perceptions of their health, severely limit daily activities, and reduce quality of life (QoL)(Bootman et al 1996).

Diabetes prevalence and incidence rates in Nigeria are rapidly rising, as is the economic burden of its complications (DeFronzo,2004). Nigeria currently faces an uncertain future in terms of the potential burden that diabetes may impose on the country. It is critical to conduct studies focusing on economic evaluations in order to make evidence-based health decisions and, as a result, offer the best risk and cost-effective treatment options, as well as a better quality of life for diabetic patients. The purpose of this study was to determine the cost-effectiveness of combined diabetes medications in T2DM patients in Ilorin, Kwara State, Nigeria.

Methodology

Settings

The study was conducted at the University of Ilorin Teaching Hospital (UITH), Ilorin, Kwara State in North-Cental Nigeria. UITH is the only tertiary hospital in the state, with a bed capacity of 600. About 50 registered pharmacists were in the employment of the Hospital. The Hospital runs a medical out-patient department comprising of a general out-patient and specialist medical out-patient clinics. Diabetes Outpatient Clinic is one of the specialist out – patient clinics

Study Population and Sample Size

Type 2 Diabetes Mellitus patients that were registered with and attended the Diabetes

Outpatient Clinic of UITH were the subjects for this study. Their population was obtained from Medical Record Department, totaling 824. Fischer's Formula was applied to determine sample size from this estimate. The required minimum sample size was 276 with inclusion of the 5% attrition rate.

Inclusion criteria covers only Type 2 Diabetes Mellitus out-patients who were registered with Diabetes outpatient clinic and on medication therapy, regardless of sex and concurrent illness. Inclusion criteria also covers Type 2 Diabetes Mellitus patients that have been on drug therapy for at least one year and adult of 18 years and above. Type 2 Diabetes Mellitus patients below 18 years of age, pregnant and lactating were excluded from this study.

Ethical Clearance

Ethical approval was obtained from Research and Ethics Committee of UITH. The approval number was ERC/PAN /2022 /03/0249.

Study Design

Drug utilization review

This part of the study was a retrospective review of antidiabetic regimens among Type 2 Diabetes mellitus patients lasting a period of 3 months. Systematic random sampling method was adopted using sampling interval of 5 for case notes from Medical Records department. In all, a total of 276 case notes were sampled. Treatment Options / Drug utilization pattern of the various treatment options available was identified from case-notes of the subjects.

Cost effectiveness analysis

Cost Measure

Total Cost of a Treatment Option = Mean Cost per Defined Daily Dosage (DDD) x Duration of Therapy. Mean cost/DDD of treatment options available at UITH was used (to avoid bias, average cost of available generic equivalents were considered for all the treatment options).

Effectiveness measure

A cross-sectional study in which the EQ-5D-5L instrument (EuroQol.EQ-5D-5L 2019 and Umpierrez et al. 2006). was used to assess the health related quality of life of a sample of patients with T2DM. The EQ-5D-5L measures the patient's overall health state in a descriptive system ofhealth-related QoL states consisting of fivedimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) eachof which can takes one of five responses rangingfrom no problems to extreme problem(EuroQol.EQ-5D-5L 2019 and Umpierrez et al. 2006) EQ-5D-5L is a valid and reliable instrument for assessing health related quality life hence utility scores (EuroQol.EQ-5D-5L 2019 and Umpierrez et al. 2006).

The health related quality of life estimates obtained was then converted into a single utility, synonymous to effectiveness (QALYs).

Data Collection Procedure

The selected patients from the retrospective review were coded with the assigned hospital numberson each of the selected 276 case notes, and the appointment days of each patient noted. Our team were present on all appointment days, identified the patients with case note numbers/code and administered the questionnaires at the point of entry of each patient into the consultation rooms.

Data Analysis

The utility values were presented as mean ± standard deviation (SD).

The means of the utility values (effectiveness) of the 3 regimens were subjected to one way ANOVA. All statistical tests were considered significant at $p \leq 0.05$. Data analysis were performed using SPSS version 20 (IBM Corporation, Armonk, NY, USA).

The utility value (effectiveness) obtained for the regimens were compared to determine which regimen was more cost effective.

Results

Anti-Diabetic Drug Utilization /Identification of Treatment Options for Cost - effectiveness Analysis in UITH

One hundred and seventy eight (64.49%) of the 276 subjects were on Metformin + Glimepiride combination therapy, fifty-two (18.84%) subjects were on Metformin + Linagliptin combined therapy while the remaining forty-six (16.67%) subjects were on metformin + Pioglitazone therapy. There was statistically significant difference between these proportions (P=0.001985; df=2)(Table 1).

Table 1 Antidiabetic regimens for Drug Utilization/Identified Treatment Options for Cost Effectiveness Analysis (n=276)

Therapy Regimen	Option Nomenclature	Number of Patients	Percentage (%)
Metformin & Glimepiride	A	178	64.49
Metformin & Linagliptin	B	52	18.84
Metformin & Pioglitazone	C	46	16.67

P=0.001985df=2

Cost Effectiveness Analysis (CEA) of Metformin + Linagliptin compared with Metformin + Glimepiride in the management of Type 2 DM.

There was statistically significant difference in the costs and effectiveness of Metformin + Linagliptin compared with Metformin + Glimepiride. Metformin + Glimepiride was not dominated but an ICER of 823.16 was obtained, as shown in table 2

Table 2 Cost Effectiveness Analysis (CEA) of Patients on Metformin + Linagliptin compared with Patients on Metformin + Glimepiride in the management of Type 2 DM.

Treatment Option	Total Cost (C) in dollars (US$)	Effectiveness *(QALY)	AverageCost Effectiveness ($/QALY)	*ICER ($/QALY)
Regimen A (Metformin 1g b.d& Glimepiride 2 mg b.d) x 3/12	23.42	0.755	$31.02/unit of effectiveness	823.16 cost per extra unit of effectiveness of
Regimen B	54.7	0.793	$68.98/unit of	

(Metformin 1g b d & Linagliptin 5 mg o.d) x 3/12			effectiveness	regimen B

P=0.0015812,df=1*QALY - Quality Adjusted Life Years. *ICER-Increamental Cost Effectiveness Ratio

Cost-Effectiveness Analysis of Metformin + Pioglitazone compared with Metformin + Glimepiride in the management of Type 2 DM.

There was statistically significant difference in the costs and effectiveness of Metformin + Pioglitazone compared with Metformin + Glimepiride. Regimen C was dominant compared to regimen A, making it more cost effective.(table 3)

Table 3 Cost-Effectiveness Analysis of Metformin + Pioglitazone compared with Metformin + Glimepiride in the management of Type 2 DM.

Treatment Option	**Total Cost (C) in dollars (US$)**	***Effectiveness (QALY)**	**CEA ($/QALY)**	**ICER ($/QALY)**
Regimen A (Metformin 1g b.d + Glimepiride 2 mg b.d) x 3/12	23.42	0.755	$31.02/unit of effectiveness	-25.78, Dominated
Regimen C (Metformin 1g b.d + Pioglitazone 30 mg o.d) x 3/12	21.77	0.819	$26.58/unit of effectiveness	

P=0.0018800,df=1*QALY - Quality Adjusted Life Years.
*ICER-Increamental Cost Effectiveness Ra

Sensitivity Analysis of Metformin/Linagliptin, Metformin/Pioglitazone compared with Metformin/ Glimepiride in the Management of Type 2 Diabetes mellitus

Sensitivity analysis indicated that decision still remain valid justifying the cost effectiveness of both Metformin + Linagliptin and Metformin + Pioglitazone when compared with Metformin + Glimepiride.as shown on table 4

Table 4 Sensitivity Analysis of Metformin/Linagliptin, Metformin/Pioglitazone compared with Metformin/ Glimepiride in the Management of Type 2 DM

	Option Nomenclature			
Sensitivity	**A Metformin/ Glimepiride**	**B Metformin/Linagliptin**	**C Metformin/Pioglitazone**	***ICER**
Effectiveness	**0.755**	**0.793**	**0.819**	
Increase cost by 25%	29.275	68.375	27.2125	B compared to A= 1,028.95/per extra unit of effectiveness C compared to A= -$32.24 (dominant)
Increase cost by 50%	35.13	82.05	32.655	B compared to A= **$** 1,234.74/per extra unit of effectiveness

				C compared to A= -**$**38.67 (dominant)
Decrease cost by 25%	17.57	41.025	16.33	B compared to A= **$**617.24/per extra unit of effectiveness C compared to A= -**$**19.38 (dominant)
Decrease cost by 50%	11.71	27.35	10.89	B compared to A= $411.6/per extra unit of effectiveness C compared to A= -$12.81 (dominant)
Cost of the regimens	**23.42**	**54.7**	**21.77**	
Increase Effectiveness by 25%	0.944	0.991	1.02	B compared to A= $665.5/per extra unit of effectiveness C compared to A= -$21.71 (dominant)
Decrease Effectiveness by 25%	0.57	0.59	0.61	B compared to A= $1, 564/per extra unit of effectiveness C compared to A= -$41.25 (dominant)

*ICER-Increamental Cost Effectiveness Ratio

Discussion

Combination therapies arecommonly and currently being used by many physicians who believe inaggressive control of blood sugar. Although the standardtreatment guidelines in diabetes mellitus still advocate theaddition of a second drug after initial trial of monotherapy,the practice of prescribing combination therapies as initialtherapies have been advocated in many studies and has becomean increasingly common practice(Suleiman and Tayo 2001). Findings ofantidiabetic drugs utilization in the current study showed consistent use of combinations of oral hypoglycemic agent in the treatment of diabetes. This is in agreement with previous a study where it was stated that, the treatment of diabetes with a combination of drugs is a cost-effective use of resources (Ekwunife et al 2016).

There was a statistically significant difference in the effectiveness (outcome) of Metformin + Linagliptin, compared with Metformin + Glimepiride, with Metformin + Linagliptin being more effective. This finding is consistent with their documented efficacy, glucose—lowering effect dependent on basal blood sugar, safety, convenient daily dosing and no dosage adjustments with hepatic and renal impairment.

Cost Effectiveness Analysis revealed that Metformin + Linagliptin prescribed, was more cost-effective than Metformin + Glimepiride. Metformin + Linagliptin first appeared to be less cost effective but $823.16 obtained which is the cost per extra unit of effectiveness of Metformin + Linagliptin was still far less than the GDP/capita in Nigeria which is US$2, 097, making it affordable(World Health Organization2003). and more cost effective than Metformin + Glimepiride in the management of Type 2 DM. This finding can be related to the outcomes of a recent study that found that more cost effective antidiabetic agent would result in significant reduction in burden of health of diabetes mellitus which has been widely reported to

be very high (Campbell et al 2016). Both drugs were efficacious in reducing the glycemic parameters as expected, and the drug combinations are approved and established drugs in the management of DM (Campbell et al 2016). When compared with other groups, they were comparable in modulating the glycemic parameters without any significant difference in efficacy. However, a recent study found the treatment pathway with Linagliptin as cost effective second line therapy compared with Glimepiride from the US health care payer perspective (Kwon 2018). Another study found Saxagliptin to be more cost effective than Glimepiride as a second line therapy with fewer adverse effects when added to metformin in type 2 diabetes in China (Shuyan et al 2015). Similar findings was demonstrated where Vidagliptin/Metformin increased drug costs compared with Gimepiride/Metformin but Vidagliptin based combination appeared to be dominant to glimepiride in terms of both cost per LY and cost per QALY gained (EuroQol. EQ-5D-5L 2019).

Contrary results were obtained by a systemic review and meta-analysis which shows the glimepiride/metformin to be more cost effective despite slight differences in adverse effects (Ikeda et al 2015). Meta-analysis concluded that the glimepiride/metformin combination, both due to cost as well as effectiveness and safety, might be the preferential treatment for most type 2 DM (Ikeda et al 2015). Similar findings have been documented (Jelsma *et al* 2003)There have been no direct comparison for cost effectiveness of Linagliptin with Glimepiride as combination therapy with metformin in Nigerian type 2 DM patients. So, this study was undertaken to evaluate the relative cost-effectiveness of these two combination therapies. The result of this study is significant because it suggest that more cost-effective antidiabetic therapies are now increasing being prescribed especially to the elderly who may benefit greatly from them. The finding in the present study also provides evidence-based information that could be used to change prescription practice and reduce prescription of less cost effective drugs.

There was a statistically significant difference in the effectiveness (outcome) of Metformin + Pioglitazone compared with Metformin + Glimepiride. Metformin + Pioglitazone was more effective. This finding is consistent with the known fact that various pathophysiological factors contribute to hyperglycemia, which inevitably requires combining antidiabetic agents with different mechanisms of action to successfully manage Type 2 DM (Kalra et al 2018).Recent recommendations have suggested patient centered glycemic management, albeit without specific recommendations regarding the optimal second-line antidiabetic agents. Insulin resistance is a major pathophysiological factor that influences Type 2 DM. Improving insulin sensitivity is extremely important in its managementBrian & Charles (2014). Thiazolidinediones (TZD) have been recognized as a true insulin sensitizer, Quinn et al. 2008) however, safety concerns were raised regarding the use of rosiglitazone which has led to TZD being used infrequently.

Cost Effectiveness Analysis revealed that Metformin + Pioglitazone was more cost-effective than Metformin + Glimepiride. Metformin + Pioglitazone was found to be dominant and more cost effective. This is similar to the finding that addition of Pioglitazone to metformin for patients with type 2 DM resulted in a similar decrease in

HBAIc levels to that induced by the addition of glimepiride (Kousoulakou*et al.*2017).. However, in addition to the comparable level of glycemic control, Pioglitazone provided several better outcomes such as improvements in lipid control, insulin resistance and hypoglycemic risk making it a highly cost effective drug in the management of type 2 DM patients not adequately controlled by metformin monotherapy (Kousoulakou*et al.*2017). This is contrary to the findings that demonstrated that Glimepiride based combination is of equal effectiveness in improvement of glycemic control as with Pioglitazone and when compared with pioglitazone, glimepiride is associated with faster glycemic control, and reduced short term health care costsAmateet al.(2015). The difference in the outcome of the current study and the previous study Amate et al.(2015) might be based on the parameters used to measure effectiveness. While the previous study was based on clinical outcomes, the current study was based on humanistic outcomes as perceived by the patients.

The results of the current study support the reported fact that cost effectiveness analysis could help to make decisions about whether new drugs should be included in a drug formulary list where decisions are made. These decisions are made based on the principle that if a drug is not better than a comparable product, it should not cost more, if it is superior to existing therapies but more expensive (a common situation) and funds are available, any extra expenditure should represent "value for money".

It is important to study the costs and benefits of the existing glucose-lowering agents, to help clinicians and decision makers choose the most cost-effective treatments. Type 2 DM treatment is a life-time condition that often requires a sequential use of drugs to ensure intensive glycemic control. Thus, it is of value to conduct economic evaluations based on life-long treatment strategy, to evaluate the therapies used by a patient from the start of medication to the end of life. This could help us comprehensively understand the impacts of different treatments on disease burden of patients.

Metformin/Glimepiride was found to be less cost-effective than combinations of metformin/Linagliptin and metformin/ Pioglitazone in the treatment of type 2 diabetes.

Institutional Treatment Guideline for anti-diabetic therapy and Hospital Drug Formulary based on cost-effectiveness couldbe developed using this and/or similar research methodology. This pharmaco-economic approach is presently lacking in Nigerian public and private Hospitals. The work provides evidence based information that could be used to change prescription practice- irrational prescription of less cost-effective anti-diabetics over more cost-effective ones, by using the information for educational intervention at prescribers' and managerial levels. The resultant effect will be cost savings in drug therapy. The use of valid economic evaluation methods to measure the value and impact of new services can increase acceptance of such programs by the medical profession, third party payers and consumers.

Financial support and sponsorship
Nil.

Conflicts of interest
There were no conflict of interest.

References

Amate, J.M., Lopez-Cuadrado, T., Almendro, N., Bouza, C., Saz-Parkinson, Z., Rivas-Ruiz, R., & Gonzalez-Canudas, J. (2015). Effectiveness and safety of glimepiride and iDPP4, associated with metformin in second line pharmacotherapy of type 2 diabetes mellitus: systematic review and meta-analysis. *Int J Clin Pract, 69(3),* 292-304.

Bootman JL, Townsend RJ, Mc Ghan WF (1996). Pharmcoeconomics in: A systematic review of randomized clinical trial in Canada In: Canadian Self CareIndustry Profile of Non-Prescription Drug Manufacturers Association of Canada, Canada p 1-208.

Bootman JL, Townsend RJ, Mcghan WF. Principles of pharmacoeconomics. (2nd ed.), Cincinnati: Harvey Whitney, 1996. 409p.

Brian, O., & Charles, E., C. (2014). Drug use indicators in patients with type 2 diabetes in a tertiary healthcare facility in Nigeria. *International Journal of Pharmacy and Pharmaceutical Sciences, 6(11),* 493-495.

DeFronzo, R.A. (2004). Pathogenesis of type 2 diabetes mellitus. *MedClin North Am, 88,* 787-835.doi:10.1186/1478-7954-1-11.

Ekwunife OI., Ezenduka, C.C., & Uzoma, B.E. (2016). Evaluating the sensitivity of EQ-5D in a sample of patients with type 2 diabetes mellitus in two tertiary health care facilities in Nigeria.

EuroQol. EQ-5D-5L about. The Netherlands 2019. https://euroqol.org/eq-5d-instruments/eq-5d-5labout/.

Gauvreau CL, Ungar WJ, Köhler JC, Zlotkin S (2012). The Use of Cost-Effectiveness Analysis for Pediatric Immunization in Developing Countries. Milbank Q 90(4): 762–790

Ikeda S, Shiroiwa K Igarashi A, et al. Developing a Japanese version of the EQ-5D-5L value set. *Health Medical Sciences.* 2015; *64:* 47–55 (in Japanese).

JA, Palmer AJ, Venn A, Sharman M, Otahal P, Neil, A. A head-to-head Campbell comparison of the EQ-5D-5L and AQoL-8D multi-attribute utility instruments in patients who have previously undergone bariatric surgery. *Patient.* 2016; 9(4): 311–22.

Jelsma J, Hansen K, De Weerdt W, De Cock P, Kind P. How do Zimbabweans value health states? *Popul Health Metrics.* 2003; 1(1):11.

Kalra, S., Bahendeka, S., Sahay, R., Ghosh, S., Md, F., Orabi, A., Ramaiya, K., et al. (2018). Consensus Recommendations on Sulfonylurea and Sulfonylurea Combinations in the Management of Type 2 Diabetes Mellitus - International Task Force. *Indian J Endocrinol Metab. 22(1),* 132-157.

Kennedy DA, Hart J, Seely D (2009). Cost Effectiveness of Natural Health Products: A Systematic Review of Randomized Clinical Trials Evid

Based Complement Alternat Med. 6(3): 297–304.

Kesselheim AS, Avorn J, Sarpatwari A (2006). The High Cost of Prescription Drugs in the United States Origins and Prospects for Reform JAMA. 316(8):858-871.

Kousoulakou, H., Hatzikou, M., Baroutsou, V. *et al.* Cost effectiveness of vildagliptin versus glimepiride as add-on treatment to metformin for the treatment of diabetes mellitus type 2 patients in Greece. *Cost Eff ResourAlloc15,*19 (2017).

Kwon, C.S., Seoane-Vazquez, E. & Rodriguez-Monguio, (2018) R. Cost-effectiveness analysis of metformin+dipeptidyl peptidase-4 inhibitors compared to metformin+sulfonylureas for treatment of type 2 diabetes. *BMC Health Serv Res* **18,** 78.

Mc Ghan W (1993). Pharmaco-economics In: Remington Text Book of PharmaceuticalSciencethand Practice of Pharmcy. 19 edition. Mack Publishing Company, Easton Pennsylvania p19291930

Quinn, C E et al. (2008) "Thiazolidinediones: effects on insulin resistance and the cardiovascular system." *British journal of pharmacology* vol. 153,4: 636-45. doi:10.1038/sj.bjp.0707452

Ray M (1979). Pharmaco-economics In: Remington, A. Text Book of PharmaceuticalScience and Practice of Pharmacy19 edition. Mack publishing Company, Easton Pennsylvania, p1931-1933.

Scaria S, Raju R, Joseph S, Mohan A, Nair AA. Pharmacoeconomics: principles, methods and Indian scenario. *International Journal of Pharmaceutical Science Review and Research.* 2015; 34(1): 37-46.

Shuyan Gu, Jing Deng, Lizheng Shi, Yiming Mu &Hengjin Dong (2015) Cost-effectiveness of saxagliptin vs glimepiride as a second-line therapy added to metformin in Type 2 diabetes in China, Journal of Medical Economics, 18:10, 808-820, DOI: 10.3111/13696998.2015.1049542

Suleiman IA, Tayo OI. Pharmocoeconomic evaluation of streptomycin versus ethambutol in the treatment of tuberculosis in Lagos University Teaching Hospital. *Nigerian Quarterly Journal of Hospital Medicine*. 2001; 11(1-4): 3-7.

Umpierrez G., Issa, M., &Vlajnic, A. (2006). Glimepiride versus pioglitazone combination therapy in subjects with type 2 diabetes inadequately controlled on metformin monotherapy: results of a randomized clinical trial. *Curr Med Res Opin, 22(4),*751-9.

Walker R, Whittlesea C. Clinical Pharmacy and Therapeutics. (5th ed.), Churchill Livingstone, (Edinburg): Elsevier Ltd; 2012.

Wertheimer, A.I. (2014). The Importance of Pharmacoeconomics. *Journal of Pharmacovigilance, 2(1),* 1000e115.

World Health Organization.(2003) Making choices in health: WHO guide to cost-effectiveness analysis/ edited by T. Tan-Torres Edejer … [et al.]