An evidence based model to consolidate Medication Adherence Cost Estimation: the MACE framework

The MACE framework

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Abstract:

Aim: To develop a standardised framework determining the economic impact of medication non-adherence.

Methods: Secondary analysis of existing literature reported cost data, aggregating cost outcome indicators. Weighted average cost analysis performed, determining the proportional contribution to total cost.

Results: Direct costs were reported in 92% of studies and indirect costs in 4% of studies. Three most utilised cost categories were hospital (68%), primary care (18%) and pharmacy costs (72%). Average unadjusted direct costs ranged $625-154,203 contributing to 88% of the total cost; adjusted medical costs ranged $565 to $56,313 representing 96% of the total cost.

Conclusion: The medication adherence cost estimation framework enables the comparison of costing studies, facilitating informed health policy decision-making based on consistent evidence and terminology.

Keywords: health economics, health policy, pharmacoeconomics, non-adherence

Introduction

Medication non-adherence is a growing epidemic with the literature and policy makers identifying it as a major clinical and economic concern[1-4] costing governments and healthcare providers $US100-290 billion annually[5]. The major findings from the World Health Organisation (WHO) report 'Adherence to Long-term Therapies – evidence for action' indicates that 1) the consequences of medication non-adherence compromise effective treatment, decrease quality of life and increase healthcare costs, 2) increasing the effectiveness of adherence interventions will have a greater impact on patient health than improving medical treatment and 3) health systems need to evolve to meet the changing needs of patients[6]. These findings have set the stage for significant growth in medication adherence research, including economic evaluations.

Economic evaluations are defined as 'the comparative analysis of alternative courses of action in terms of both their costs and their consequences'[7], and are conducted to inform healthcare resource allocation[8]. While all economic evaluations assess costs, the combination of cost outcome indicators (i.e. the types of costs that are included) and the methods used to calculate these costs exhibit substantials heterogeneity[9,10]. Evaluation of the costs associated with medication non-adherence within single disease studies (e.g. Osteoporosis, HIV) as well as comparisons across diseases and studies highlights the existing heterogeneity in methodological processes, leading to wide spanning results[11]. In Osteoporosis the annual adjusted cost of medication non-adherence across studies ranges from $949 to $44 190[11] per person while across multiple disease studies the range spanned $949 to $52 341[11] per person. Additionally, there is no gold standard in the method used to estimate adherence, with selection of the calculation of adherence usually being based on study attributes, clinical setting or resource availability, ultimately resulting in a range of differing methods, cut-off points and recommendations[12].

Given the cost burden associated with medication non-adherence, it is valuable to develop interventions which aim to reduce costs[13-21]. The global medication adherence technology and intervention market continues to expand, valued at $1.6 billion in 2016 and forecasted to reach $3.6 billion by 2023[22], with numerous interventions designed to improve medication non-adherence across clinical conditions. Despite such growth inconsistency in the reporting of medication non-adherence has resulted in only some interventions relating to better adherence and health outcomes[23]. A lack of consistency in costing methodological approaches serve as a major limitation moving forward in adherence research[12]. Standard approaches in terminology and reporting guidelines have been established through development of the ABC taxonomy representing the gold standard for defining medication adherence behaviour across three stages and the EMERGE guidelines which outline the minimum reporting criteria that should be considered in every publication about medication adherence[24-29]. However, limited guidelines have been developed to standardise the way medication non-adherence costs are measured and reported in economic evaluations[30]. Often complete adherence is assumed or it is assumed that adherence in clinical trials is the same as real-world adherence when establishing clinical effectiveness[31]. This

often leads to overestimation of adherence and cost effectiveness[32]. Hilligsmann et al, outlines this concept in Osteoporosis where poor (real-world) adherence to oral bisphosphonates resulted in a doubling of the incremental cost effectiveness ratio (ICER) compared with perfect (assumed) adherence levels (€3,909 vs. €10,279 respectively)[32,33].

A review of the literature carried out by Hughes et al in 2001[34] and updated in 2007[30] exploring the methodologies that may be appropriate for incorporating non-adherence and non-persistence in economic evaluations demonstrates that substantial inconsistency remains in the definitions adopted, and methods and inputs used in pharmacoeconomic evaluations. Moving forward this paper aims to streamline and provide structure to the types of costs that should be included when determining the economic impact of medication non-adherence. The key cost outcome indicators that contribute the greatest proportion to total costs have been incorporated into the newly proposed medication adherence cost estimation (MACE) framework. This facilitates the inclusion of key cost outcome indicators associated with medication non-adherence into economic evaluations, enabling greater clarity in the economic comparison of adherence intervention studies to allow the establishment of meaningful conclusions across studies.

The aim of the research is twofold: (1) determine what cost outcome indicators are reported in the literature and the weighting they contribute to overall costs, (2) develop a new framework to rationalise the estimation of the cost of medication non-adherence utilising the identified cost outcome indicators.

Methods

Secondary analysis of data reported in a recent systematic review "Economic impact of medication non-adherence by disease groups- a systematic review" was undertaken to identify cost outcome indicators utilised to report the economic impact of medication non-adherence. The review quantified the cost of medication non-adherence across different disease groups. Studies reporting the cost of medication non-adherence were included, with costs defined as any cost outcome indicator associated with medication non-adherence that was quantified with a monetary value in the original study. Studies only reporting the measure of effect of healthcare utilisation in relation to adherence were excluded, as they provided no cost value. The protocol for the systematic review is available through the PROSPERO international prospective register of systematic reviews database (CRD42015027338) and the full methodology was outlined in Cutler et al[11].

Phase 1: Extraction and Classification of Costs

Phase 1 consisted of extraction of the classification of cost outcome indicators demonstrating the economic impact of medication non-adherence[11] through assignment of a monetary value to an input associated with medication non-adherence. A cost outcome indicator was defined as a category of costs that was associated with medication non-adherence, e.g. hospital costs encompass all costs associated with a hospital admission attributable to medication non-adherence. Cost outcomes were classified according to the terminology utilised in the reported study. The following data was extracted: cost outcome indicator, monetary value assigned to each indicator, definition of the cost outcome, cost classification (e.g. direct or indirect) and disease state[11]. Three quantifiable stages of medication adherence were assessed utilising the ABC taxonomy classification system, categorising study measures in relation to initiation, implementation and discontinuation[24]. Initiation was defined as the first dose of a prescribed medication; participants were required to be medication naïve or reinitiating the medication regimen. Implementation describes the extent to which the prescription was taken as prescribed among the initiated cohort, examined through measures such as medication possession ratio and proportion of days covered. Discontinuation signifies the end of therapy, when a dose is omitted and no subsequent doses are taken thereafter, measured through medication gaps and time to discontinuation[24].

Phase 2: Comparison and Aggregation of Cost Outcome Indicators

Phase 2 consisted of the development of a matrix to facilitate the comparison of cost outcome indicators. The content of each related outcome, as assessed by analysis of original definitions of indicators were aggregated into subcategories. Cost outcome indicators that were classified differently but had the same definition were grouped. Costs were classified as adjusted or unadjusted based on original study reporting. All costs were converted to $USD2018 monetary values and reported per patient per annum.

Phase 3: Weighted Average Analysis

Phase 3 consisted of the statistical analysis of the cost outcome indicators to determine what core set of costing outcomes contributed the greatest proportion to total healthcare expenditure. Only studies that reported cost outcome indicators in addition to total costs or total healthcare costs were included for weighted average analysis. Monetary values reported for each cost outcome per study were extracted. The minimum, maximum and average value for each indicator were determined. A weighted average for each cost outcome indicator was calculated by multiplying the percentage of studies that included that cost component by the average cost of each indicator as a proportion of the studies total cost. A ranking of the cost indicators was then created to determine the relative importance of certain cost outcome indicators based on previously conducted studies.

Results

A descriptive synthesis of the extracted data was performed and cost outcome indicators were identified. Given the heterogeneity in approaches used to classify cost outcome indicators of medication non-adherence, a framework outlining the key cost outcome indicators that contribute the greatest proportion to total healthcare expenditure was derived. This highlighted the core set of cost outcome indicators that have contributed substantially to the total cost of medication non-adherence.

Extraction, classification and aggregation of cost outcome indicators

Across 79 studies, 35 different cost outcome indicators were used to report the economic impact of medication non-adherence. Table 1 demonstrates the terminology used to describe the cost outcome indicators and the frequency with which these terms were identified in the literature. It further highlights the classification of cost outcome indicators into broader categories to facilitate comparison. Analysis of original study definitions facilitated the distinction between direct and indirect costs. Direct costs were reported in 92% of studies (n=73) and refer to transactions and expenditures for medical or non-medical products and services. The types of costs may include hospitalisations, prescription medications, physician fees, laboratory tests, radiological procedures as well as expenditures such as transportation, lodging, family care and home aides[35]. This core category is further subcategorised into medical costs consisting of hospital costs, primary care costs, medical test costs, and pharmacy costs in addition to direct non-medical costs. The three most utilised cost categories were hospital, primary care and pharmacy costs, 68% of studies reported hospital costs (n=54), 18% of studies reported primary care costs (n=15) and 72% of studies reported pharmacy costs (n=57). Eleven studies (13%) reported conjointly hospital, primary care and pharmacy costs, 56% (n=45) hospital and pharmacy costs, while only one study reported hospital, primary care, medical test and pharmacy costs. Indirect costs were defined as those that occur because of loss of life or livelihood and may result from morbidity or mortality[35]. Indirect morbidity costs may occur because of being absent from work, due to decreased earning ability when working or long term disability necessitating a change in work type as well as the costs associated with premature death[35]. These costs were reported in 4% of studies (n=3) and included societal costs (1%, n=1) and productivity costs (5%, n=4). Two percent of studies (n=2) examined both direct and indirect costs to evaluate the economic impact of medication non-adherence (see supplementary table 1).

Analysis of cost outcome indicators

Weighted average analysis of cost outcome indicators highlighted the categories that contributed the greatest proportion to the overall cost of medication non-adherence. Of the 79 included studies, 56 reported cost outcome indicator monetary values in addition to total cost (see supplementary table 2). Both unadjusted (86% of total cost)

and adjusted (96% of total cost) cost analysis determined that medical costs associated with hospital costs, primary care costs and pharmacy costs contributed the greatest proportion of total cost. Analysis of the unadjusted cost outcome indicator examples determined that over 88% of costs reported in the literature were direct costs associated with medication non-adherence and arised predominately from hospital costs (53%); mainly outpatient and inpatient costs (25% and 23% respectively), primary care costs (21%) and pharmacy costs (21%) (figure 2). Similarly, for the adjusted cost outcome indicators (figure 3) over 90% of the reported costs were attributed to direct costs however, primary care costs contributed the greatest proportion 53% followed by hospital costs (30%) and pharmacy costs (17%). Average unadjusted medical costs exhibited the greatest cost range variability ($585 to $152,660) and contributed on average 86% of the total costs. Within this core category, the hospital costs subgroup accounted for 53% of total costs and ranged from $457 to $151,118 while pharmacy costs subgroup represented 21% of total cost and ranged from $154 to $30,943 (figure 4). Average adjusted medical costs ranged from $565 to $56,313 representing 96% of the total cost while hospital costs (30%) and pharmacy costs (17%) ranged from $2,044 to $48,180 and $22 to $21,430 respectively (figure 5). Hospital costs accounted for the greatest proportion of medical costs within the unadjusted cost analysis (53%). In the adjusted cost analysis primary care costs contributed the greatest proportion to total cost (53%).

ABC Taxonomy Classification

Medication adherence, the process by which patient's take their medications as prescribed is classified into three components: initiation, implementation and discontinuation[24] (see supplementary table 1). Initiation marks when the patient takes the first dose of a prescribed regimen; 59% of studies reported initiation (n=47). All 79 studies examined and reported aspects of implementation (correspondence of the patient's actual dosing regimen to the prescribed regimen), while 33% of studies (n=26) reported discontinuation. Persistence, a measure of adherence signifying the length of time between initiation and discontinuation was reported in 22 studies.

MACE framework

The MACE framework (table 2) relies on two core elements, making a clear distinction between direct and indirect costs. Two core cost outcome indicators emerged from the data (direct and indirect costs), with a further 7 subcategories (hospital, primary care, medical test, pharmacy, direct non-medical, societal and productivity costs) and 35 cost outcome indicator examples. The categories were derived from the 35 cost outcome indicators identified across 79 studies, with the indicators not being exhaustive to those outlined in the framework but serving as a guide for potential expenses that fall within each category.

MACE Framework Definitions

1. Direct costs

The first core element is *direct costs* and refers to any cost incurred due to resource use that are completely attributable to the use of a healthcare intervention of illness. These costs can be split into direct medical costs and direct non-medical costs. Direct medical costs include the cost of a defined intervention and all follow up costs for other medication and healthcare interventions in ambulatory, inpatient and nursing care. All physician and specialist care, including rehabilitation, emergency care as well as treatment or prevention of an injury, illness or disease, including the costs of testing, procedures, therapies and medications[35]. It is further categorised into hospital, primary care, medical test and pharmacy costs.

Hospital costs refer to the costs associated with the act or incidence of receiving medical care or aid at a hospital. This includes but is not limited to inpatient admissions, outpatient services, acute care and emergency department visits. Additionally it incorporates all medical services (e.g. medication, imaging, pathology, specialist care) that are provided within the hospital setting.

Primary care costs refer to healthcare and utilisation of healthcare facilities provided in the community, outside the hospital setting for diagnosis, prevention, advice or treatment of an injury, illness or disease. This includes GP visits, ancillary care, psychiatric assessment, interdisciplinary team management, targeted case management, social worker visits, home helps and volunteer workers.

Medical test costs entail the costs of all medical procedures performed to detect, diagnose or monitor diseases, injury, susceptibility and determine a course of treatment e.g. laboratory tests, radiology costs, pathology results.

The *pharmacy cost* element incorporates utilisation rates and corresponding costs associated with obtaining prescription and non-prescription medication in the community setting in addition to the provision of pharmacist services. It takes into account both disease specific and medication costs associated with comorbidities, where reported. Costs associated with prescribed medications, health aides, non-prescription medication, over the counter medications and any out-of-pocket expenses are measured.

Direct non-medical costs are expenditures as the result of an illness but are not involved in the direct purchasing of medical services. These include expenditures such as food, transportation, lodging, family care, home aides and clothing as a result of illness.

2. Indirect costs

Indirect costs are those that occur due to loss of life or livelihood, and may result from morbidity or mortality[36]. Mortality costs are the costs associated with premature death, while morbidity costs are associated with lost earning and productivity by the patient or caregivers[35].

241 *Societal costs* refer to the costs other than those associated with direct healthcare. These costs may not
242 have been borne by the payer or provider of the healthcare services and include arrest, incarceration, opportunity
243 costs of resources used and time spent seeking and receiving care[37]. In addition this subcategory also considers
244 costs incurred by society as a result of the additional use of time and resources. It incorporates the costs imposed
245 on society as a consequence of levies, taxes and charges[38,39].

246 The second subcategory, *productivity* costs, represents the additional cost burden placed on workplaces
247 and employers due to a loss of productivity. It considers the impact medication non-adherence has on an
248 individual's capacity to work; they may work less than they otherwise could, retire early, be absent from work
249 more often, have lower productivity while at work, or die prematurely[40]. Additionally, informal carers may also
250 work less or not work at all in order to care for non-adherent patients. *Productivity costs* capture the lost earnings
251 and production due to non-adherence in terms of absenteeism (prolonged absence from work), disability pensions
252 (financial help due to medical conditions that prevent one from working), premature death, early retirement,
253 unemployment, reduced working hours and presenteeism (reduced capability in completing tasks in an efficient
254 manner).

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Discussion

Increasing scarcity of healthcare resources, diminishing health budgets and increasing healthcare costs are compelling decision makers to choose between alternative healthcare interventions. Increasingly the cost-effectiveness of interventions and overall healthcare gain to the population are important to determine the allocation of competing resources[41]. As the main goal of health economic analysis is to aid decisions, it is imperative that these evaluations are comparable in terms of the cost outcome indicators that they include to estimate the cost burden of medication non-adherence. Despite the growing evidence of models and methods examining the integration of medication adherence into pharmacoeconomic evaluations, limited consistency and uniformity exists in the methods and terminology used to estimate the cost outcome indicators. This dissimilarity has resulted in the generation of an array of concepts and terms being utilised in a variety of combinations to determine the economic impact of medication non-adherence. The definitions of the cost outcome indicators used vary and partially overlap, resulting in conceptual confusion, and contributing to methodological weaknesses in the field. Further methodological problems arise from the disparity in identification, measurement and valuation of non-adherence costs[42].

A framework identifying reported cost outcome indicators from 79 reviewed studies was constructed facilitating the analysis of original studies reporting the economic impact of medication non-adherence in addition to total cost[11]. Cost outcome indicators that contributed the greatest proportion to total cost, formed the structure categorisation of the framework. The MACE framework was developed to provide a streamlined approach to estimate the cost of medication non-adherence. Lack of such a system has resulted in the heterogeneous reporting of over 35 different cost outcome indicators, making the comparison of studies difficult and deficient. The consolidated framework will allow a more complete evaluation of the economic impact whilst simultaneously facilitating the comparison across studies and disease states. Use of the MACE framework (table 2) will enable understanding of terms that appear to be different but incorporate the same cost components. Thus, it aids in the interpretation and comparison of studies that may have used different terminology to classify similar or the same cost outcome indicators. We attempted to minimise complexity by providing clear and concise category descriptions and examples. This resulted in an aggregated system containing two core categories, seven subcategories and an extensive list of examples of cost outcome indicators. The framework provides a guide to cost estimation and can be applied in its entirety or utilising only those categories that are relevant to the study objectives. Additionally, validation of the framework is required to test and advance its viability. Applying the framework to both retrospective and intervention based studies across a range of disease states is required to ratify the proposed framework. Moving forward examining the application of the MACE framework across varying perspectives (e.g. government, health care, pharmaceutical industry and patient) may prove valuable in gaining a better understanding of the economic burden of medication non-adherence globally.

Assessment of study methodologies and identification of significant heterogeneity across classification of cost outcome indicators, in addition to a varied mix of reporting styles made the statistical analysis of data challenging [10]. Due to the substantial variation in cost outcome indicators reported, the missing data and lack of reported standard deviations of costs a weighted average cost analysis was chosen to report the findings. Analysis of cost outcome indicators revealed that three key cost components contributed the greatest percentage to overall total cost. These three cost outcome indicators were grouped into 'medical costs' of the proposed framework. While ideally all cost categories should be taken into consideration when determining the cost of medication non-adherence, it stems to reason that the most influential costs that need to be considered are medical costs; particularly inpatient, outpatient, pharmacy costs and medical expenses incurred in the community setting e.g. GP visits. These costs contribute to over 85% of the cost of medication non-adherence. While these costs make up the largest proportion of total cost, further investigation is required to determine the economic impact of indirect costs on medication adherence, as many studies fail to evaluate these costs. However, Drummond et al stipulates that it is not worth investing time into the evaluation of costs that are so small they are unlikely to make a difference in the study results. It may be worthwhile identifying these cost categories, yet the estimation of them need not be pursued[7]. Depending upon the perspective of the economic evaluation it may be important to measure both direct and indirect costs.

Awareness of the different degrees and types of non-adherence are important when analysing cost data[43]. The impact of non-adherence on, as well as the relevant levels of non-adherence for healthcare costs can vary across disease states with certain medications exhibiting greater 'forgiveness' than others[42,44]. The three dimensions of adherence; initiation, implementation and discontinuation should be taken into consideration when assessing costs associated with medication non-adherence[24]. Additionally, the differences in relevant costs from different perspectives emphasise the importance of specifying the point of view from which the cost calculation is performed[42]. Which costs and consequences count, and how they should be measured and valued, depends on what type of decision makers in healthcare are intended to be informed by the economic evaluation[7]. The most valid cost data in terms of real resource use is collated via measuring every single cost item in detail and valuing it according to market price[45]. However, this may not be feasible as many economic evaluations are conducted using summary data, such as costs in the literature from previously conducted studies. In this instance individual patient data is not available and how the data has been summarised will determine whether resource quantities can be separated from prices to conduct the analyses[7]. The MACE framework facilitates the analysis of both direct and indirect costs, some or all of the categories may be relevant depending on the perspective of the analyses being conducted. Reporting across the two core categories supports transparency in the data, allowing the reader to derive results that are relevant for their own purpose whilst simultaneously facilitating the establishment of comparisons between studies. Similarly, the condition for which the economic evaluation is being estimated is of significant importance with certain conditions carrying a greater cost burden then others. In cancer direct costs have been reported to be the smallest portion of total costs per patient[46] while in diabetes one

study conservatively estimates direct costs to account for 66% of total costs[47]. Alternatively, in schizophrenia one study estimated non-medical costs to account for 65% of healthcare expenditure; 15% attributed to direct non-medical costs and 50% attributed to indirect/productivity costs[48]. These variations need to be taken into consideration when comparing studies utilising different cost outcome indicators and when comparing across conditions.

The medication non-adherence cost burden is multidimensional in nature traversing healthcare professional groups, governments and individuals. However, the degree of visibility medication adherence occupies within the health policy context remains less than ideal, often being overshadowed by other health policy issues due to incongruence in demonstrating impact[49]. In order for funding or reimbursement for medication adherence to be introduced, convincing and comparable evidence on the cost and benefits of medication adherence support needs to be stipulated. This framework attempts to homogenise the cost findings, enabling clear communication with policymakers to stimulate concerted action to address the economic impact of medication non-adherence[49]. When used in conjunction with existing validated guidelines and frameworks for health outcomes research (e.g. ABC taxonomy, CHEERS, TIDier, EMERGE) it will provide evidence to evaluate the clinical and cost-effectiveness of interventions to address medication non-adherence, building a strong case for investment[8,24,28,49,50].

Conclusion

Economic evaluation can be used to assess the effectiveness of interventions and inform health policy. In order to guide policy makers on how to best allocate limited healthcare resources in the most efficient and effective manner, it is imperative that a comparable method be developed to accurately estimate the economic impact of medication non-adherence. The MACE framework streamlines the current disarray of cost outcomes that exists in the literature. It provides structure via building on the existing foundations to create a classification system taking into account direct and indirect costs, that can be used in its entirety or partially dependent upon the perspective of the intended audience. Moving forward, future research would be recommended to test, validate and advance the MACE framework. The adoption of this framework will help to standardise the cost outcome indicators utilised, hereby facilitating health policy decisions based on consistent evidence, terminology and reporting standards.

Summary Points

Background

- Medication non-adherence places significant economic and clinical burden on patients, governments and healthcare systems.
- Heterogeneity exists in the methods and cost outcome indicators used to report and measure the economic impact of medication non-adherence.
- The medication adherence cost estimation framework is a newly proposed model to consolidate the monetary valuation of medication non-adherence through determination of the cost breakdown of related cost outcome indicators described in the literature.

Methods

- Secondary analysis of existing literature reported cost data was conducted to aggregate cost outcome indicators and their associated monetary value.
- A weighted average cost analysis was performed to determine the proportion each indicator contributed to total cost. Indicators were ranked to determine their relative importance in relation to total cost and the medication adherence cost estimation framework was developed through utilisation of these rankings.

Results

- The MACE framework proposes costs should be classified into two core categories direct and indirect costs, with further sub-categorisation into hospital, primary care, medical test, pharmacy, direct non-medical, societal and productivity costs.
- The three most utilised categories to report the economic impact of medication non-adherence were hospital costs (68%), primary care costs (18%) and pharmacy costs (72%).

Conclusion

- The MACE framework streamlines the current disarray of cost outcomes that exists in the literature.
- The adoption of this framework will help to standardise the cost outcome indicators utilised, hereby facilitating health policy decisions based on consistent evidence, terminology and reporting standards.

Figure and Table Legends

Figure 1 Unadjusted cost outcome indicator contribution to total cost. Line represents the minimum, maximum and average percentage contribution for each core category and subcategory towards total cost. Single points indicate only one cost value, reported for that category.

Figure 2 Adjusted cost outcome indicator contribution to total cost. Line represents the minimum, maximum and average percentage contribution for each core category and subcategory towards total cost. Single points indicate only one cost value, reported for that category.

Figure 3 Unadjusted cost range $USD2018. Line represents the minimum, maximum and average cost reported for core categories and subcategories. Single points indicate only one cost value, reported for that category.

Figure 4 Adjusted cost range $USD2018. Line represents the minimum, maximum and average cost reported for core categories and subcategories. Single points indicate only one cost value, reported for that category.

Table 1 Literature reported cost outcome indicators. Percentage composition of cost outcome indicator examples used to quantify ($) medication non-adherence throughout the literature. “Economic impact of medication non-adherence by disease groups: a systematic review,” by Cutler et al, 2018 *BMJ Open;*8:e016982. doi: 10.1136/bmjopen-2017-016982

Table 2 Medication adherence cost estimation (MACE) framework. Outlines core cost categories, subcategories and cost outcome indicator examples. Cost data adapted from “Economic impact of medication non-adherence by disease groups: a systematic review,” by Cutler et al, 2018 *BMJ Open;*8:e016982. doi: 10.1136/bmjopen-2017-016982

Supplementary table 1 Cost outcome indicators reported and ABC taxonomy classification.

Supplementary table 2 Studies identified with medication non-adherence costs reported by cost outcome inidcator and total cost. 56 of 79 studies reported cost outcome inidcators in addition to total cost. Cost data adapted from “Economic impact of medication non-adherence by disease groups: a systematic review,” by Cutler et al, 2018 *BMJ Open;*8:e016982. doi: 10.1136/bmjopen-2017-016982

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