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Conducting cost-effectiveness analyses of type 2 diabetes in low- and middle-income countries: can locally generated observational study data overcome methodological limitations?

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ABSTRACT

In low- and middle-income countries, the high personal and economic burden of type 2 diabetes is further compounded by inadequate resources for diabetes care when compared with high-income countries. Health technology assessments (HTAs) aim to inform policy decision makers in their efforts to achieve more effective allocation of resources by providing evidence-based input on new technologies. Within the hierarchy of evidence, randomized controlled trials (RCTs) remain the 'gold standard' used to inform HTAs, but are limited by poor external validity (ie, generalizability to real-world populations). Unlike RCTs, observational studies are able to enrol broader patient populations, but their design renders such studies vulnerable to confounding factors and selection bias. However, it is increasingly recognized that observational studies can complement RCTs by supporting and extending efficacy findings from RCTs to real-world clinical practice, particularly across geographical populations. They can also provide locally relevant baseline and disease natural history data to populate health economic models. Thus, observational data are likely to be of considerable informative value to policy makers in developing countries reaching decisions on diabetes care within an environment of scarce resources.

1. Introduction

Most people with type 2 diabetes live in less-developed countries [1]. The rapid growth of non-communicable diseases (NCD) in general, and diabetes in particular, has the potential to put severe strain on healthcare systems in low- and middle-income countries [2–5]. The personal burden of diabetes is also immense, and is shared between those with diabetes and their families as carers [1]. Unlike advanced economies, three quarters of the disability burden attributable to NCD in low- and middle-income countries occurs between the ages of 15 and 69 years [6]. Despite the

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high economic impact of diabetes in developing countries, advanced economies account for 90% of global expenditure for diabetes care [1].

An aging population, improved life expectancy, and the obesity epidemic are some of the reasons for the increasing burden of diabetes. However, mounting expenditure can also result from policy decisions, notably from the adoption of new technologies and from expanding insurance coverage to facilitate the epidemiological transition.

There is a need for greater allocation of healthcare expenditure to be directed at diabetes care in particular in low- and middle-income countries [1,7]. Effective allocation of resources, however, remains a significant challenge to any healthcare system given the need for long-term (several decades) planning of demand for services, the effectiveness of new technologies, and the likely benefits versus costs of implementing intervention programs [8,9].

2. Defining 'value for money'

Having reached a decision to intervene against the escalating burden of diabetes, policy makers will conduct technology assessments to assess value for money. Many of the techniques used to improve the standard of clinical care, pioneered through evidence-based medicine, have migrated into the realm of policy as health technology assessments (HTAs) [10]. The overarching aim of HTAs is to inform policy decisions by providing structured and evidence-based input on new technologies [10], sometimes known as evidence-based policy making.

Considerations of efficacy and safety are key factors governing treatment selection decisions for clinicians, but healthcare policy makers must make choices at the aggregate level under conditions of overall resource scarcity. Economic evaluations assess the comparative 'value for money' of health interventions compared with the next best alternative (marginal analysis), while budget-impact analysis assesses the 'affordability' of introducing new health technologies in ring-fenced health budgets [11,12]. The lost opportunity cost of poor healthcare investments is higher for developing countries.

Weak information systems compound the difficulty of generating economic evaluations, as real-world clinical practice trends, hospital and primary care costs, complication costs and high levels of out-of-pocket costs, and informal payments complicate the picture. A lack of local cost data is a particular problem for low- and middle-income countries as few of these countries have diagnostic-related group-based healthcare payments. As a result, studies evaluating diabetes costs in these countries are relatively scarce [7,13].

The most common forms of economic evaluation employed are cost-effectiveness analyses and cost-utility analyses, which measure health benefits using mortality estimates (life-years gained) or quality-adjusted life-years gained (QALYs). Costs are normally evaluated as direct costs (ie, excluding lost work productivity) from the perspective of a 'third-party payer' such as a public insurer, private insurer, or health maintenance organization.

The World Health Organization (WHO) is trying to develop standardized methods for cost-effectiveness analyses across interventions and geographical regions. The WHO CHOosing Interventions that are Cost-Effective (CHOICE) program advocates the use of gross domestic product (GDP) as a common unit of cost measurement across nations and suggests the applications of a cost-effectiveness threshold, below which good value for money as cost per QALY is between one and three times the GDP per capita [14]. This concept has been utilized recently in South Korea [15].

3. Data sources for health economic (HE) models

Data modeling is inevitable when endeavouring to capture the costs and benefits of a new technology throughout the lifetime of a patient. In reaching decisions on healthcare interventions, policy makers require the best available evidence, but also that which reflects real-world practice [16]. Two main strategies are employed to obtain HE data for models, namely the collection of existing data through systematic literature review, or alternatively the collection of HE data obtained in the context of a clinical trial [17].

The sources for clinical effectiveness estimates are derived from the best available data, which are typically randomized controlled trials (RCTs), but may otherwise be observational studies, case-control reports, or expert opinion. RCTs compare the efficacy and safety of a medication versus placebo or an active comparator using pre-defined clinical endpoints and in a controlled environment [18]. In contrast, observational studies can adopt a cohort or case-control design. In case-control studies, the effect of a treatment is compared in groups with and without the outcome of interest, whereas in cohort studies a selected group of patients are prospectively observed over a specific length of time for a clinical outcome [18]. Patient-level sources for observational studies include medical records and claims databases.

Whether a modeling or trial-based approach is adopted, the specific data required for the economic evaluation are the same (Table 1) [19].

To improve the quality of estimated endpoints from the models, a 'hierarchy of evidence' is typically adopted, with good quality RCTs and meta-analysis of quality RCTs at the top of the hierarchy, and expert opinion of good clinical practice at the lowest level. Despite limitations of 'external validity', RCTs remain the 'gold standard' used to inform HTAs [20]. In low- and middle-income countries, national (and ethnic)-specific RCT data are seldom available. Nevertheless, there is a tendency to use international RCT data irrespective of their established limitations in terms of resource use transferability [21].

3.1. *RCTs versus observational studies*

As summarized in Table 2, the characteristics of RCTs versus observational studies have been subject to extensive discussion across therapeutic boundaries [20,22,23].

RCTs maintain high internal validity by adopting such measures as strict inclusion and exclusion criteria to screen patients entering the study, a concealed randomized design

Table 1 – Data required in economic evaluations.

Data required	Data source
Comparative treatment effects	Usually RCTs If projection of long-term outcomes is required, a modeling approach is used
Consumption of healthcare resources between comparator groups	Either obtained concurrently during an RCT or from sources such as routine statistics, DRG, local surveys, naturalistic studies, patient-chart reviews, and expert opinion
Costs of resources	Observational studies or routine data collection
Effects of treatment on quality of life	Generally obtained in phase 4 quality of life research or during an RCT
Health state preference	Either during an RCT, a specific utility study, or from surveys of the general population

DRG = diagnostic-related groups, RCT = randomized controlled trial.

(to prevent selection bias), and strictly controlled treatment conditions [16,18,20,24]. The main objective of the RCT design is to verify that ensuing clinical findings are attributable to differences between an active treatment and placebo or comparator. However, the conditions under which RCTs are conducted, including the rigid treatment protocols, regular follow-up visits, and additional patient support provided by the research clinical professionals, limit the generalizability of findings from RCTs to routine clinical care [18]. Improved compliance among patients participating in RCTs is a particular example of the discrepancy between RCTs and 'real-world' clinical practice, and may explain the lower uptake of insulin therapy (median of 8 years to initiation of insulin therapy) in an observational study based on patient records compared with an RCT that showed 51% of patients began injectable insulin at the first study visit [16].

Observational studies, on the other hand, are not constrained by the narrow patient selection criteria used in RCTs and are generally able to enrol a broader patient population, which enhances their generalizability [16,18]. Patients with serious comorbidities, for example, are routinely excluded from RCTs but can be included in observational studies, which enables results from the latter studies to more accurately reflect the general clinical setting than trial findings. One such example is the three-fold higher mortality rate estimated in a validated type 2 diabetes epidemiological model compared with the PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive), which may be largely attributed to the exclusion of patients with comorbidities in the RCT [16]. Observational studies, however, carry a risk of low internal validity due to the potential for selection bias and the wide range of confounding factors in the population [19,25]. The non-randomized aspect of the observational study design can render comparisons between studies vulnerable to confounding due to differences in patient characteristics such as illness severity. Thus, observed differences between study outcomes may reflect variations in patients' clinical and demographic characteristics rather than a true treatment effect [18].

RCTs are likely to provide an unbiased indication of treatment effect, but data for other important parameters such as baseline events, health-related quality of life, and resource use are less likely to be subject to selection bias if derived from observational studies [20].

To reliably estimate costs and outcomes over a patient's lifetime, HE models require long-term outcome data. This is a particular challenge with NCDs and the often long duration of disease. RCTs typically provide data within a limited timeframe [12,24]. As a result, 'surrogate' or intermediate endpoints are often employed to extrapolate short-term clinical

Table 2 – Characteristics of randomized controlled trials (RCTs) and observational studies.

RCTs	Observational studies
Utilize surrogate endpoints (the association between change in surrogate endpoints and final outcome remains inconclusive)	Utilize patient-reported endpoints
High internal validity (ie, reproducibility) due to randomized design, strict selection criteria, and controlled conditions – enables detection of true treatment difference	Low internal validity due to non-randomized nature and inclusion of broad-ranging patient characteristics – potential for selection bias and masking of true treatment effect
Low external validity (ie, applicability to 'real-world' environment) as a result of restrictive inclusion and exclusion criteria, strict treatment conditions, more follow-up visits and contact with healthcare practitioners than 'real-world' setting	High external validity due to the inclusion of a broader patient population (eg, patients with comorbid conditions)
Shorter length of follow-up limits detection of rare adverse events	Generally longer follow-up, which allows detection of rare adverse events
Less useful for the collection of data on resource use	More amenable to the collection of data on resource use

endpoints to long-term patient outcomes, frequently using a modeling approach [19,24]. For example, in clinical studies of insulin analogs, estimation of long-term outcomes required the establishment of a relationship between glycemic control or body mass index and long-term outcomes such as mortality, cardiovascular endpoints, peripheral microvascular complications, diabetic neuropathy, and diabetic nephropathy [26]. However, HTA agencies advise caution with respect to the exclusive use of surrogate outcomes, until valid evidence, such as those from RCTs and systematic reviews, have shown a consistent association between the surrogate endpoint and the final outcome for the health technology of interest [27]. In a recent review of 35 UK HTA reports, only one report showed level 1 evidence (RCT) of a strong association between the change in surrogate endpoint (biopsy-confirmed acute rejection) and change in the final outcome (graft survival), while two reports provided level 2 evidence (observational studies), and a further study provided level 3 evidence (review) [28].

Observational studies, by virtue of their design, can also be used to determine findings for surrogate endpoints, but additionally can address the limitations of RCTs with respect to identification of adverse events as a result of short duration of drug exposure [18,19]. Longer study evaluation periods and the inclusion of a larger and more diverse patient population (including patients with concomitant comorbid conditions) render observational studies more amenable to the detection of adverse events, including rare treatment complications [18].

4. Enhancing the role of observational studies in HE evaluations

RCTs are, and will remain, the cornerstone of HE evaluations in advanced healthcare systems. However, an analysis of the UK NHS Economic Evaluation Database reported that one-third of economic evaluations recorded since 1994 were based on a single RCT [20]. Although observational studies have traditionally been considered to be methodologically weaker than RCTs, there is increasing awareness that observational studies can provide a complementary role to RCTs by supporting and further extending efficacy findings from RCTs to large patient populations in real-world clinical practice [18]. In low- and middle-income countries, observational studies may form the primary data source for economic evaluations. In addition to phase 3 trial programs, clinical endpoints relevant to economic models can be collected as part of post-marketing surveillance research.

With the growth in number of HTA agencies worldwide, it has become evident that economic evaluations used to inform HTAs are not generalizable between countries [29,30]. This has been largely attributed to differences in healthcare resource availability, clinical practice, and relative costs [30]. This poses a particular problem in trial-based economic evaluations where resource use and perhaps costs may be evaluated concurrently with efficacy measures and pooled across study sites, as the resulting data may not be applicable to a specific location [30]. In this setting, evidence from observational studies could 'bridge the gap' for the translation of results from RCTs to country-specific populations, as, for example, information with respect to the prevalence of illness severity and patient comorbidity within an RCT may not reflect that of the local general population [16]. Considering the importance of real-world relevance, a 3-step successive modeling approach has been suggested, which comprises assessment of internal validity, external validity (real-world relevance), and net impact at the level of the healthcare system [31]. This approach has been used to evaluate the informative value to policy decision makers of an RCT conducted in people with benign prostatic hyperplasia [31].

5. Long-term health outcome and HE models in diabetes

Internationally, there are a number of HE models that have been developed to quantify the long-term outcomes of diabetes. HE models (for example, The Center for Outcomes Research [CORE] Model and The United Kingdom Prospective Diabetes Study [UKPDS] Outcomes Model) have been derived from data obtained in large outcomes studies such as the UKPDS [8,26,32–34] and Diabetes Control and Complications Trial (DCCT) .

The UKPDS outcomes model, developed from patient-level information obtained in UKPDS, is a computer simulation that uses proportional hazard modeling to predict the risk of first occurrence of major diabetes-related complications (ischemic heart disease, myocardial infarction, heart failure, stroke, blindness, renal failure, and amputation) in patients with type 2 diabetes [32]. Another established model is the CORE type 1 and 2 diabetes HE model, which constitutes a series of inter-dependent Markov models that simulate the progression of 15 diabetes-related complications: angina, myocardial infarction, congestive heart failure, stroke, peripheral vascular dementia, diabetic retinopathy, macula edema, cataract, hypoglycemia, ketoacidosis, lactic acidosis, nephropathy and end-stage renal disease, neuropathy, foot ulcer and amputation, and other-cause mortality [33,35]. The model accounts for costs, screening, and treatment strategies for microvascular and macrovascular complications, as well as treatment practices for end-stage complications [33]. A recently-introduced HE model is the Archimedes Model, which uses a mathematical approach to recreate detailed information on demographics, symptoms, treatment, resources, and outcomes for people with type 1 and 2 diabetes [35].

These HE models have demonstrated validity in different geographical populations [8,26,32–34,36]. However, a recent meeting of computer modellers (Mount Hood Challenge Meetings) highlighted the need for further improvements in existing HE models for diabetes [35]. In this meeting, eight modeling groups (including groups responsible for the UKPDS, CORE, and Archimedes models) participated in a series of challenges to simulate the outcomes of a type 1 diabetes (DCCT) and type 2 diabetes (Collaborative Atorvastatin Diabetes Study [CARDS]) clinical trial. On the basis of the findings from these challenges, it was highlighted that there are methodological variations between these established diabetes HE models that warrant further attention.

6. Conclusion

The high personal and economic burden of type 2 diabetes in low- and middle-income countries is compounded by inadequate resources for diabetes care when compared with high-income countries. Observational data are likely to be particularly valuable for informing healthcare policy makers in developing countries to formulate appropriate diabetes treatment pathways, encourage the optimal allocation of scarce resources, and improve aggregate patient outcomes.

Conflict of interest

All authors were members of the A_1chieve study advisory board and received support from Novo Nordisk to attend advisory board meetings. Prof. SeiHyun Baik has authored an article sponsored by Sanofi-Aventis but reported no other conflicts of interest. Prof. Antônio Roberto Chacra has served as a consultant (Advisory Board), received research grants and honorarium for lectures from Novo Nordisk, MSD. Eli Lilly, Bristol-Myers Squibb, AstraZeneca, Novartis, Pfizer, Sanofi-Aventis and Roche. Prof. Li Yuxiu reported no other conflicts of interest. Jeremy White was employed by Novo Nordisk International Operations A/S at the time of writing. Dr. Serdar Güler reported no other conflicts of interest. Prof. Zafar A. Latif reported no other conflicts of interest.

Authorship

All authors made substantial contributions to the conception and design of the study or the acquisition of data. All authors had the opportunity to critically review the manuscript during development and the final draft of the manuscript was approved by all authors prior to submission.

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