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Cost-effectiveness of a complex continuum of care intervention targeting women and children: protocol for an economic evaluation of the Bukhali trial in South Africa

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ABSTRACT

Introduction As nearly two-thirds of women presenting at their first antenatal visit are either overweight or obese in urban South Africa, the preconception period is an opportunity to optimise health and offset transgenerational risk of both obesity and non-communicable diseases. This protocol describes the planned economic evaluation of an individually randomised controlled trial of a complex continuum of care intervention targeting women and children in Soweto, South Africa (Bukhali trial).

Methods and analysis The economic evaluation of the Bukhali trial will be conducted as a within-trial analysis from both provider and societal perspectives. Incremental costs and health outcomes of the continuum of care intervention will be compared with standard care. The economic impact on implementing agencies (programme costs), healthcare providers, participants and their households will be estimated. Incremental cost-effectiveness ratios (ICERs) will be calculated in terms of cost per case of child adiposity at age years averted. Additionally, ICERs will also be reported in terms of cost per quality-adjusted life year gained. If Bukhali demonstrates effectiveness, we will employ a decision analytical model to examine the cost-effectiveness of the intervention over a child's lifetime. A Markov model will be used to estimate long-term health benefits, healthcare costs and cost-effectiveness. Probabilistic sensitivity analyses will be conducted to explore uncertainty and ensure robust results. An analysis will be conducted to assess the equity impact of the intervention, by comparing intervention impact within quintiles of socioeconomic status.

Ethics and dissemination The Bukhali trial economic evaluation has ethical approval from the Human Ethics Research Committee of the University of the Witwatersrand, Johannesburg, South Africa (M240162). The results of the economic evaluation will be disseminated in a peer-reviewed journal and presented at a relevant international conference.

Trial registration number Pan African Clinical Trials Registry (PACTR201903750173871; https://pactr.samrc.ac.za).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ By embedding this economic evaluation within a randomised controlled trial, this study will provide rigorous evidence on the cost-effectiveness of interventions that begin preconception and aim to improve both maternal and child health.
⇒ The period of follow-up is longer than for other related interventions and allows us to study the effects of the intervention from the preconception stage until children reach age 5 years, covering crucial stages of child development.
⇒ The richness of the data collected allows a better understanding of the effects of the intervention on secondary outcomes such as consumption patterns and caregivers' time allocation, which enables identification of the societal costs of the intervention.
⇒ However, power calculations were not possible for household cost data collection, which will instead rely on a pragmatic sample.
⇒ Uncertainties may also remain in long-term effectiveness and cost-effectiveness, given uncertainty on whether impact on weight is maintained into adulthood and beyond.

INTRODUCTION

Low-income and middle-income countries (LMICs) bear a disproportionate burden of non-communicable diseases.[1] For example, the prevalence of type 2 diabetes mellitus doubled between 1980 and 2014 in sub-Saharan Africa, India and China, and exceeds prevalence in high-income countries.[1] These countries also have high prevalence of infectious diseases, and persistent maternal and child malnutrition.[2] In South Africa, the nutrition transition has led to a high obesity burden, especially among women.[3] Estimates from 2016 indicate that 68% of women ≥15 years were overweight or obese (OWO), rates being higher in urban areas.[4] In Soweto, an

urban township in Johannesburg, prevalence of OWO among men was found to be stable at approximately 10% from childhood to adulthood. However, among women, this was found to increase from 10% to 43% from ages 8 to 22 years.[5] Additionally, a 2013 national survey finds a high combined prevalence of OWO in children 2–5 years old at 22.9%,[6] considerably higher than the global prevalence of OWO.[7] This is concerning since early childhood is a crucial period for predicting obesity in adolescence.[8]

Higher weight gain in preconception and interpregnancy periods is associated with higher risk of gestational diabetes mellitus (GDM), pre-eclampsia and large-for-gestational-age babies.[9] Nearly two-thirds of pregnant women in Soweto at first antenatal clinic visit were OWO; 10% were diagnosed with GDM in late pregnancy.[10] There is a strong association between high maternal pre-pregnancy weight and the likelihood of children being OWO.[11 12] Childhood weight gain, OWO and adiposity are risk factors for poor health and development trajectories over the life course.[13 14] A meta-analysis found that obese children are around five times as likely as non-obese children to be obese in adulthood (pooled relative risk 5.21, 95% CI: 4.50, 6.02).[15] However, the only measure of obesity in any included study was body mass index, which is limited by not measuring body fat, but rather presumed excess weight based on height. More recently, another study found that 67% of obese children 5 yeas old were obese in adulthood, and that children who were obese at age 5 years had a fat mass index at age 50 years that was 4.15 units lower when compared with children who were a normal weight at age 5 years.[16] Optimising health from preconception onwards with a life course intervention rooted in the Developmental Origins of Health and Disease framework[17–19] could positively impact the future health of women and children, and prevent intergenerational risk in South Africa and similar settings.

Dean *et al*[20] identify and review 23 randomised controlled trials (RCTs) of preconception interventions. The interventions improved women's health behaviours, and had a positive impact on maternal, neonatal and child health outcomes. However, none of the studies were conducted in Africa or explored the impact on child development outcomes. There are no known economic evaluations of comparable interventions. A 2021 systematic review of economic evaluations on preconception care interventions found eight studies of preconception interventions focusing on nutrition management, folic acid supplements and counselling with participants.[21] Every study concluded that the intervention was either cost-effective or cost-saving. However, none of the interventions combined nutritional support and counselling, none looked at child outcomes and only two focused on the general population, the rest targeting women with diabetes. Additionally, the only study to include LMICs was a modelling study looking at wide range of interventions in 75 countries.[22] Finally, another systematic review of economic evaluations on preconception care interventions identified eight studies, mostly related to screening interventions.[23] The authors highlight a particular need for evidence on the equity impact of such interventions.

More broadly, there is also limited evidence on the cost-effectiveness of interventions addressing health or development in early childhood, either as standalone interventions or combined packages. A 2015 review identified only six studies of cost-effectiveness of undernutrition improvement in LMICs.[24] No studies assessing the cost-effectiveness of early child development interventions or a combined package of early childhood nutrition and development interventions in LMICs were identified. More recently, two relevant articles have been published.[25 26] However, the studies enrolled participants after the child was born and consider child outcomes only for a maximum of 24-month follow-up. This leaves a gap in the evidence base about the costs, cost-effectiveness and affordability, as well as equity impact of interventions beginning preconception that aim to improve maternal and child health. Without adequate evidence on costs and cost-effectiveness, it is challenging for stakeholders to compare the relative value of investing in different interventions and to allocate resources to competing priorities in a changing epidemiological landscape. This study aims to address these gaps, with a view to inform resource allocation to such programmes.

The Bukhali trial

The Bukhali trial is a two-arm individual-randomised (1:1) RCT. Participants are randomised to the intervention arm or 'standard of care plus' control arm. All participants will be exposed to the preconception component of the intervention, or the control, for a maximum of 18 months. Participants who become pregnant during this period are monitored throughout pregnancy and the postnatal period. Participants who do not become pregnant exit the study. Participants in the control arm have access to standard care offered through the public health system, and are also provided with a non-health-specific 'life skills' curriculum via telephone to minimise attrition, given the long follow-up period of the trial. The trial is described fully elsewhere.[27] This article outlines the methodology used in the economic evaluation of the trial.

Objectives

The objectives of the economic evaluation of the Bukhali trial are to:

- Estimate the total cost of delivering the intervention from the provider and societal perspectives.
- Estimate the incremental cost and cost-effectiveness of the intervention compared with standard care from the provider and societal perspectives.
- Measure the equity impact of the intervention.

METHODS AND ANALYSIS

Study setting and population

Bukhali is being implemented in the Chris Hani Baragwanath Academic Hospital in Soweto, South Africa. Formative research conducted with trial participants

highlights insecure and unstable economic conditions in this setting.[28] Participants were recruited through a household survey. The study area was divided into 30 clusters and the study team systematically recruited eligible participants by visiting homes (ie, door to door) in these clusters. Eligible participants were then enrolled into the trial after providing written informed consent process in person, and an appointment was made for them to attend the hospital for baseline data collection and randomisation. All consenting women 18–28 years old are eligible to participate, unless they have a diagnosis of type 1 diabetes, epilepsy or intellectual disability.

Intervention

The Bukhali trial aims to develop and test a complex four-phase intervention to optimise maternal health, and child health and development through infancy and early childhood.[29] Bukhali has four intervention phases, beginning at preconception and following through pregnancy, infancy and early childhood. The intervention is delivered by community health workers through individual in-person sessions at the hospital, in addition to further support by phone. Each intervention phase consists of health literacy resource materials, micronutrient supplements and sessions to support behaviour change using Healthy Conversation Skills.[30 31] Recruitment targets a sample of 6800 women, to reach a target of 1530 pregnancies. An 'index child' conceived after randomisation will receive the intervention (or control programme), in accordance with the trial arm their mother was randomised to.

The intervention phases are summarised in figure 1. Trial recruitment was completed in early 2023 (n=6371). Data collection for early childhood outcomes (5 years) will be completed in 2029.

Measurement of health outcomes

Participants will be followed up until the index child reaches 5 years of age, and outcome data on physical health and development will be collected at the end of every intervention phase to assess impact. The primary outcome of the trial is dual-energy X-ray absorptiometry-derived fat mass index (fat mass divided by height squared) in the child at age 5 years (ie, child adiposity at age 5 years). Secondary child outcomes include developmental and behavioural outcomes and secondary maternal outcomes include physical and mental health outcomes and health-related behaviours. Composite health-related quality of life outcome measures will also be collected using the EQ-5D from women after delivery and the EQ-5D-Y Proxy from women on behalf of their child at the 60-month follow-up.[32] Outcomes are assessed at nine time points in total, the first at baseline and the last at 5 years of age. The assessment schedule is outlined in detail in the trial protocol.[27] The extent and pattern of missing outcome data will be assessed. If outcome data are missing at random, multiple imputation will be used to maximise sample size and statistical power.

Identification, measurement and valuation of resource use

Cost and cost-effectiveness analyses will be conducted from the provider perspective, accounting for the costs incurred by the provider in the provision of the interventions and from the societal perspective, which also includes costs borne by families and the wider societal impact of changes in health outcomes. Provider costs will

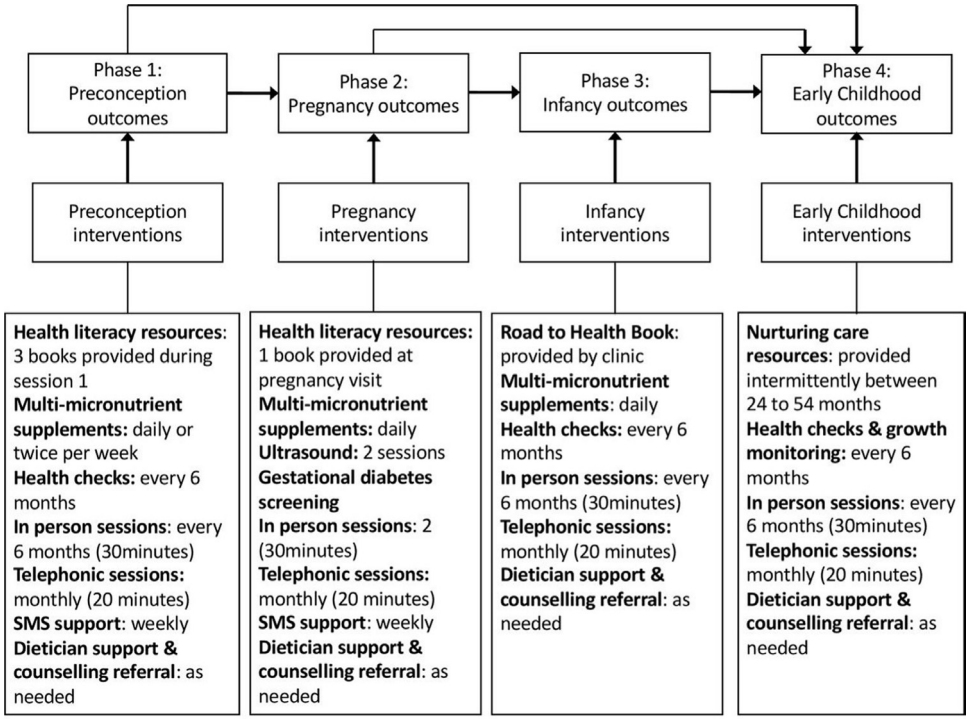

Figure 1 Bukhali intervention phases and components. SMS, Short Messaging Service.

Table 1 Cost category, potential cost impact and data sources

Cost category		Hypothesis/potential cost impact	Proposed data source(s)
Provider	Intervention costs for designing, starting up and implementing the Bukhali intervention (programme costs)	► Direct increase in costs in the short term due to equipment, staff costs, training costs, educational material, etc that are additional to standard care	► Project financial records ► Project staff time sheets ► Project staff interviews
	Changes in utilisation of health services (provider costs)	► Bukhali intervention may increase care-seeking behaviour, as responsive caregiving and health literacy increase ► Conversely, the intervention could reduce costs of care-seeking due to improved physical health of the index child	► System costs associated with providing standard care (MoH budget reports, published literature) ► Care-seeking and associated costs survey
	Lifetime costs of adiposity (provider costs)	► In the long term, health service provider savings associated with reduced adiposity diagnosis and improved long-term health outcomes	► Trial measures of adiposity ► System costs associated with providing standard care (MoH budget reports)
Societal	Households' or users' costs of participation (household costs)	► Changes in household consumption due to adoption of intervention messages around diet and caregiving practices ► Changes to out-of-pocket costs of care-seeking ► Opportunity cost of participating in the intervention ► Opportunity cost of behaviour change	► Household consumption survey ► Care-seeking and associated costs survey ► Caregiver time use survey ► Published wage estimates
	Lifetime costs of adiposity (societal costs)	In the long term, societal savings associated with reduced adiposity diagnosis and improved long-term health outcomes	► Trial measures of adiposity ► Published estimates of economic impact of overweight and obesity

MoH, Ministry of Health.

be incurred by the University of the Witwatersrand and the public healthcare system. An overview of cost data is presented in table 1.

Programme costs are incurred by the institutions implementing the Bukhali intervention: the University of the Witwatersrand and the Gauteng Provincial Department of Health. Data for these costs (henceforth, programme costs) will be based on financial project accounts prospectively collected from each institution. Programme costs include the costs incurred during intervention start-up and implementation and will capture all costs associated with designing and implementing the Bukhali intervention.

Additionally, the intervention could affect how frequently mothers and children fall sick, the severity of each illness episode and the type of care sought. The intervention may reduce the prevalence of illness (either absolutely or in term of severity), which would lead to reduced costs of care-seeking. However, conversely, the intervention also promotes responsive caregiving and health literacy, and therefore could increase the likelihood of seeking care. We will test whether the intervention leads to changes in care-seeking and associated costs. Such costs will be borne by the provider and households. Provider costs will be estimated based on published data and Ministry of Health budget reports. For households, a healthcare utilisation survey will be designed to measure healthcare use in the previous 6 months for both the mother and child, and will include both direct and indirect (eg, transportation) costs of healthcare. Expenditure on the mother's healthcare, expenditure on the child's healthcare and total expenditure on healthcare will be directly compared across intervention and control arms.

Other household costs will also be measured. First, behavioural changes promoted by the intervention may also affect how household resources are allocated to food and non-food consumption.[33 34] For example, mothers may be given information on reducing the consumption of calorie-dense but nutritionally poor consumables, such as sugar-sweetened beverages. Thus, participants and households may incur direct costs of participation in the intervention and shift their expenditure from such consumables to other food or non-food items. A survey that measures both food and non-food expenditure will be designed and administered. Expenditure in intervention and control arms of the trial will be described and compared directly to explore differences in total consumption, total food consumption and total non-food consumption. Second, the intervention requires a time commitment through the uptake of encouraged new, optimal caregiving behaviours and activities. Participants need to assimilate new information and allocate

sufficient time to engage with the intervention, and to adopt new behaviours and activities into their regular routines.[35] Individuals facing competing demands on their psychological, physical and time resources often return to familiar habits and behaviours if they feel that these resources are constrained.[36] A time-use diary will be developed to capture the way caregiver participants allocate their time between different activities over a 'normal' day. Time spent on different activities will be directly compared across intervention and control arms. Published wage estimates will be used to value participant time when estimating the opportunity cost of intervention participation.

Finally, overweight and obesity have significant economic impact. One study estimated total societal costs of overweight and obesity of US$6 billion in South Africa in 2020.[37] The impact of the Bukhali intervention on societal costs of overweight and obesity will be estimated based on outcomes collected and secondary data.

Annual programme costs will be collated on a customised Microsoft Excel tool, divided into sections for different cost components, including staff, materials, capital and joint costs. Joint costs are those costs shared across project components, such as overheads and administration costs, and will be allocated to programme components based on both staff time sheets and key informant interviews with representatives of each institution. The economic analysis will exclude research costs. Financial costs will be converted to economic costs. For example, relevant donated goods will be assigned a current market value in the costing tool.

For all household costs (ie, consumption, time-use and care-seeking), analyses will be conducted at the end of each intervention phase to align with the unblinding procedures of the trial evaluation. All household costs will be measured in a pragmatic sample, which aims to include as many trial participants as possible given practical and resource constraints, at the end of each trial phase.

Economic evaluation

To determine whether Bukhali is cost-effective, affordable and the cost of delivery at scale, we will conduct base case analyses from the provider and societal perspectives alongside the trial analyses to estimate the cost-effectiveness of the intervention compared with standard care as implemented. Cost-effectiveness analysis will be conducted after completion of the final phase of the intervention. If Bukhali demonstrates an impact on child adiposity at age 5 years, we will employ a decision analytical model to examine the cost-effectiveness of the intervention over the child's lifetime. A Markov model will be used to estimate the long-term health benefits, healthcare costs and cost-effectiveness of Bukhali compared with standard care, drawing on results of the trial and available published data. The relative risk of children who are obese at age 5 years being obese in adulthood will be sourced from available secondary data, as will the health-related quality of life associated with obesity. Uncertainty in this relationship will be explored through scenario analyses making different assumptions on relative risk. Differences between trial arms in quality-adjusted life years (QALYs) will be reported for children. Total economic costs of the intervention will be presented, and incremental cost-effectiveness ratios will be reported in terms of cost per QALY gained.

For earlier phases, analysis will be in the form of a cost–consequence analysis, whereby all relevant costs and outcomes (for both mothers and children) of the interventions are tabulated without aggregating into ratios, allowing policymakers to easily compare the incremental costs and outcomes of Bukhali. Costs will be estimated cumulatively for each phase of the intervention (ie, accounting for all previous costs), while outcomes will be reported as measured at endline of each phase. We also propose combining the preconception and pregnancy phase as in our analyses as this continuum is likely to be more informative for providers and in-country stakeholders.

To assess model sensitivity to uncertainty in key parameters, a univariate sensitivity analysis will be conducted where each input parameter is varied in isolation based on assumed upper and lower limits. A discount rate of 3% will be used in the base case analysis, while alternative annual rates of 0% and 6% will be used in sensitivity analyses. Probabilistic sensitivity analysis will be conducted for the cost-effectiveness analysis, using 1000 Monte Carlo simulations to simultaneously model variation in all model parameters (ie, cost components, utility weights and transition probabilities) based on assumed distributions.

Face validity of the analysis will be assessed by an expert on life course risk of obesity. Internal validity will be assessed by rigorous checking of code for errors and through deterministic sensitivity analysis. External validity will be assessed by comparing results with available independent studies at the time of analysis. The analysis and reporting of results will also follow the Consolidated Health Economic Evaluation Reporting Standards Statement.[38]

Fiscal space analysis will be used to assess whether it is feasible for the South African government to sustainably allocate resources to the intervention within a healthcare budget.[39] Total provider costs will form the basis for affordability estimates and reported as a percentage of national gross domestic product. The total cost of a fully scaled programme will also be compared with current health spending in context.

Equity impact

By exploring whether Bukhali proportionally benefits those who have higher need, we can better understand how programmes can be targeted to achieve equitable impact and inform discussions about scale-up. The marginal mean difference in outcomes between intervention and control arms will be calculated within quintiles of socioeconomic status. Socioeconomic status will be

measured in two ways. First, using consumption expenditure collected in this study, or a composite asset index using data collected in the original trial to aid comparability with similar studies.[40] Second, using a social vulnerability index, which provides a more nuanced understanding of need as it considers monetary and non-monetary dimensions of deprivation, enabling differentiation between population groups who may all be relatively poor in monetary dimensions such as consumption expenditure or asset ownership.[41]

Patient and public involvement

Patients and public are not involved in the design or conduct of this economic evaluation study.

DISCUSSION

This article outlines the protocol for the first economic evaluation of a complex package of interventions beginning preconception that aim to improve maternal and child health. This protocol provides a transparent plan for data collection and analysis, with the aim of improving comparability with related studies. The results of this economic evaluation will be disseminated through national stakeholder meetings, conferences, peer-reviewed publications and policy briefs, and will be used to inform decision-making in South Africa. Additionally, this study will contribute to limited economic evidence on similar interventions globally. A potential limitation of the analysis is that uncertainties may remain regarding long-term effectiveness and cost-effectiveness, particularly given uncertainty over whether intervention impact is sustained into adulthood.

Ethics and dissemination

The Bukhali trial economic evaluation has ethical approval from the Human Ethics Research Committee of the University of the Witwatersrand, Johannesburg, South Africa (M240162). Informed consent will be sought from each adult participating in the study. A local language information sheet with information about the study will be read and given to participants. Understanding will be verified before consent is requested.

The results of the economic evaluation will be disseminated in the local community as well as to the scientific community, practitioners, local and international policymakers, and a wider audience in English and local languages where appropriate via (1) publications in high-impact peer-reviewed scientific journals; (2) presentations at national and international conferences; (3) non-technical policy briefs and webinar presentations; (4) integration of methodological approaches and empirical findings into teaching materials at both institutions; (5) a project website and social media channels.

Contributors TP, RL, CD, SAN and NB all contributed to the study design. SAN is is the co-PI of the Bukhali trial. CD oversees intervention and control components of the Bukhali trial and process evaluation. TP drafted the economic evaluation protocol and all authors contributed to revised drafts. TP, RL and NB will conduct the analysis. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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