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Protocol for the economic evaluation of the Care for Adolescents who Received Information 'Bout Outcomes, 2nd iteration (CARIBOU-2) non-randomised, cluster-controlled trial of an integrated care pathway for depression in adolescents

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ABSTRACT

Introduction Depressive disorders in adolescents are highly prevalent and debilitating and are a risk factor for self-harm and death by suicide. In the context of recovery from the COVID-19 pandemic, strained healthcare resources are compounded by an increased demand for treatment services for adolescents with depression. The objective of this study protocol is to delineate the proposed economic evaluation of an integrated care pathway for depression in adolescents within the Care for Adolescents who Received Information 'Bout Outcomes, 2nd iteration (CARIBOU-2) non-randomised, cluster-controlled trial.

Methods and analysis Two economic evaluations of the CARIBOU-2 trial (n=300) will be conducted—a cost-effectiveness analysis and a cost-utility analysis. In the cost-effectiveness analysis, we will examine the primary clinical outcome of the trial, change in the Mood and Feelings Questionnaire total score. In the cost-utility analysis, the clinical outcome will be quality-adjusted life-years, a generic measure of health burden. Data on the resources and respective costs required to deliver the intervention will be collected by the research team. Data on resource use post-intervention will be obtained from a mix of administrative data holdings and self-report; relevant unit costs will be obtained from existing data sources. The outcome of both economic evaluations will be the incremental cost-effectiveness ratio. Relevant sensitivity analyses will be undertaken, and cost-effectiveness acceptability curves will be produced to characterise any sources of uncertainty in the analysis. Equity considerations will also be examined, where relevant.

Ethics and dissemination Ethical approval for the larger CARIBOU-2 trial, including the economic evaluation, has been obtained by the Centre for Addiction and Mental Health as well as site-level ethics boards (019/2021; Centre for Addiction and Mental Health). All participants will provide informed consent for their data to be analysed and reported. The results of the main trial and the economic evaluation will be submitted for publication in a peer-reviewed journal and shared with relevant policy makers across Canada.

Trial registration number NCT05142683.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study will contribute to the literature on economic evaluations of interventions targeting depression in youth.
⇒ This study will inform whether an integrated care pathway is a cost-effective option to treat depression in adolescents.
⇒ Some resource use data will be self-reported and thus subject to recall bias and potentially stigma-related under-reporting bias.
⇒ The study may not capture all resources used by participants.
⇒ The utility values employed in this study will be obtained from prior related literature and not from the adolescents involved in the trial.

INTRODUCTION

Depressive disorders in adolescents are highly prevalent and debilitating and are a risk factor for self-harm and death by suicide.[1–4] In the context of recovery from the COVID-19 pandemic, increased demand for treatment services for adolescents with depression is anticipated, compounded by strained healthcare resources.[5] Determining the cost-effectiveness of interventions is necessary to inform decisions around resource allocation. However, there is a paucity of evidence on the cost-effectiveness of treatments for adolescent depression, particularly

within Canada. We undertook a scoping review of existing economic evaluations of adolescent depression interventions to ascertain any prior relevant work that had been done on the topic.[6] We found few related economic evaluations (n=10), with the majority having been undertaken either in the UK (n=4) or the USA (n=4), while the other two were undertaken in Australia and Germany. Most studies undertook an economic evaluation alongside a clinical trial (n=9), whereas only one study undertook a modelling-based economic evaluation. Of these, five were undertaken alongside trials testing cognitive–behavioural therapy (CBT) alone or CBT and selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, in combination.[7–11] One study examined the economic evaluation of a trial of a collaborative care model,[12] which involved a pre-treatment education and engagement session, after which youth (with parental input) were given the choice of CBT, antidepressant medication or both. Another study occurred alongside a trial of brief psychosocial intervention and short-term psychoanalytical psychotherapy, in addition to CBT,[13] while another examined an exercise programme.[14] Five of the 10 studies adopted the societal perspective, where all relevant costs, regardless of the payer, and opportunity costs were considered. Nine of the 10 studies examined quality-adjusted life-years (QALYs) as the main outcome of the economic evaluation. Few studies (n=2) undertook equity/subgroup analyses; these are important to undertake as decisions based on average measures of cost-effectiveness may lead to incorrect treatment recommendations for specific population groups.[15] CBT with and without SSRIs was found to be cost-effective relative to treatment as usual (TAU) in two studies, with an incremental cost-effectiveness ratio (ICER) per QALY of −$45 792 in one study[8] and ICERs per disability-adjusted life-years between $9000 and $34 000 in another.[10] The collaborative care model, compared with TAU, was also found to be cost-effective, with an ICER per QALY of $18 239.[12] In other cases where individual or combined treatment options were compared with active structured treatments, findings were mixed.[7 9 11] For example, one study from the UK reported an ICER per QALY of £102 965,[7] while another study from the USA found an ICER per QALY of −$28 833.[9] Overall, the scoping review found few studies examining cost-effectiveness of multicomponent interventions and no economic evaluation studies of interventions for adolescents with depression in the Canadian setting. Moreover, the scoping review revealed that existing studies were lacking on some elements required in an economic evaluation, such as justification around the choice of the study perspective and time horizon, the inclusion of major long-term and/or negative outcomes regarding the primary outcome measure(s), such as self-harm and suicide ideation, and engagement with patients and others affected by the study.[16 17]

The objective of this study protocol is to delineate the economic evaluation of the Care for Adolescents who Received Information 'Bout Outcomes, 2nd iteration (CARIBOU-2) intervention within the context of a non-randomised, cluster-controlled clinical trial, while building on prior related work. It is hypothesised that the CARIBOU-2 intervention will be cost-effective (ie, specifically more costly but more effective) in the treatment of depressive symptoms in help-seeking adolescents compared with TAU over a 52-week period.

METHODS AND ANALYSIS

Description of the primary study and its design

Integrated care pathways are pre-set treatment processes intended to coordinate interdisciplinary teams in the application of clinical practice guideline recommendations.[18] The CARIBOU-2 intervention is an integrated care pathway with development input from young people with lived experience and involves seven core components: (1) assessment; (2) psychoeducation; (3) psychotherapy options (where first-line treatment is CBT and second-line treatment is a brief psychosocial intervention)[9]; (4) caregiver support; (5) medication options (where first line of treatment is fluoxetine, second line is sertraline, third line is escitalopram and fourth line is duloxetine); (6) measurement-based care team reviews every 4 weeks (which involve meeting with the youth and clinicians to review measure scores and discuss treatment changes); and (7) graduation from the treatment.[19] The intervention duration is dependent on the youth's response to treatment but can be up to 52 weeks. Further details on the pathway can be found elsewhere.[19] The comparator, TAU, may or may not involve any of the following: assessment, psychoeducation, psychotherapy, medication and family work.[19] For TAU, there is no prescribed format to any of these components, nor prescribed measurement-based care. The comparator group was selected based on the US National Institutes of Health expert panel's recommendations for selecting comparator groups in behavioural interventions, particularly as it relates to the overall objective of a clinical trial.[20] The first 25 youth participants enrolled at each site will receive TAU. Subsequently, staff at sites are trained in the pathway, and the following 25 participants enrolled will be assigned to the CARIBOU intervention. Clinicians must be social workers, social service workers, occupational therapists, nurses, psychologists, psychiatrists or registered therapists to deliver the interventions. See the primary study protocol for further details.[21]

Decision problem

The CARIBOU-2 trial will measure the effectiveness of an integrated care pathway, which seeks to improve depressive symptoms in adolescents presenting to care with depression as the chief complaint. The trial-based economic evaluations will determine the cost-effectiveness of CARIBOU-2 and will be guided by the current economic evaluation guidelines recommended by Canada's Drug Agency (CDA), formerly known as the Canadian Agency for Drugs and Technologies in Health,[22] and the Consolidated Health Economic Evaluation Reporting

Standards 2022 reporting guidance for health economic evaluations.[16]

Type of economic evaluations

Two economic evaluations will be conducted. The first economic evaluation will be a cost-effectiveness analysis, which will examine the primary clinical outcome measure of the trial, change in the Mood and Feelings Questionnaire (MFQ),[23] where the MFQ screens for depressive symptoms. The second economic evaluation of CARIBOU-2 will be a cost-utility analysis (ie, a cost-effectiveness analysis where effectiveness is measured using a utility measure), in line with the CDA guidelines for the recommended reference case analysis,[22] where the outcome measure will be QALYs. The QALY is recommended in economic evaluation studies due to its ability to be compared across different interventions and illnesses/disorders.[22] Both economic evaluations will be undertaken at two time points, 24 and 52 weeks post-enrolment follow-up, using the sample with non-missing data (where adolescents who are lost to follow-up over the course of the trial or with missing data on outcomes and/or costs will be excluded) as well as the sample with imputed data.

Study population

Participant recruitment (planned n=300) will occur over 4.5 years, from February 2022 to September 2027, at four to six sites (hospitals and community-based mental health agencies) across southern Ontario and Alberta, where youth often receive outpatient mental healthcare. Adolescents will self-refer or be referred by a third party (eg, doctors, school counsellors, caregivers) to the site, and then recruited after their intake. Site staff (eg, intake workers, clinicians) will assess the youth, including the use of the MFQ[23] to screen for depression and inclusion/exclusion criteria. Informed consent will be obtained from all study participants by a study research assistant.

The trial will include adolescents between the ages of 13 and 18 years, inclusive, who express that 'depression' (or some synonym of depression) is a primary concern, where clinician or intake staff agrees that depressive symptoms are a primary treatment target, who have an MFQ score ≥22 at two sequential visits (screening and baseline assessment), who are either a new referral to the clinic in the past 3 months or, if previously received treatment at the clinic, had a period of 3 months without treatment in the past 6 months, and who are able to speak and read English. The trial will exclude youth with known or highly suspected presentations of psychotic symptoms (eg, hallucinations) that are persistent, affect functioning and have observable effects on behaviour; those with severe substance use disorder, bipolar disorder, intellectual disability, severe eating disorder and imminent risk of suicide requiring hospitalisation as per judgement of the assessing clinician; and those unable to provide informed consent to the study for any reason.

If the adolescent agrees, caregivers will also be asked to participate in the study. Other than fluency in English and capacity to make decisions regarding consenting to research, there are no other inclusion or exclusion criteria for caregiver participation.

TAU will be provided in the same hospital/community mental health agency and may or may not include referral to psychotherapy and/or parental support; psychiatric care and the use of psychotropic medication is permitted.

Perspective

We will adopt the perspective of the publicly funded healthcare payer (ie, the Ontario Ministries of Health and Long-Term Care and the Alberta Ministry of Health), in line with the CDA guidelines for the recommended reference case analysis,[22] which includes all health system costs. According to the CDA guidelines, when a broader societal perspective is of interest to the decision-maker, the impact of the intervention on time lost from paid and unpaid work by both patients and informal caregivers due to illness, treatment, disability or premature death should be included in an additional non-reference case analysis.[22] Therefore, we will also undertake an additional analysis (ie, a non-reference case analysis), where we will adopt a modified societal perspective, and caregiver time costs and lost income due to appointments will be considered, in addition to health system costs. The results of the non-reference case analysis will be reported separately from the reference case analysis for each outcome, in line with the CDA guidelines.[22] The inclusion of caregiver time costs and lost income due to appointments in the non-reference case analysis will shed light on the impact of the intervention beyond the healthcare system (ie, the reference case) as well as its impact on caregivers.

Time horizon and discounting

The time horizon of the analysis will be 52 weeks post-enrolment, the length of participant involvement in the trial. This time horizon allows time for each component of the intervention to be completed if indicated, while accounting for wait times. When the time horizon is less than 1 year, discounting is not needed.[22]

Measurement and valuation of health

The outcome of the cost-effectiveness analysis will be the change in the MFQ, a 33-item self-report measure, which screens and assesses depressive symptomatology in children and adolescents between the ages of 8 and 18.[23] The questionnaire consists of several descriptive phrases on how the adolescent has been feeling or acting over the prior 2 weeks. The coding of the MFQ reflects whether the phrase was true for the adolescent most of the time (score=2), sometimes (score=1) or not at all (score=0) in the past 2 weeks. The MFQ score ranges from 0 to 66, where cases with a score of 22 or more are suggestive of likely depression.[24]

The outcome of the cost-utility analysis will be the QALY, which is a measure that considers the health-related quality of life related to a person's health state as well as the time they spent in that given state. To our

knowledge, the MFQ has not yet been translated into QALY ratings. However, an existing review on utility values of generic preference-based instruments for children and adolescents with mental health problems[25] found that utility values reported for depression in this population ranged from 0.495[7] to 0.81.[26] Furthermore, prior work has employed utility values of 0.8 and 0.6 for mild depression and moderate to severe depression, respectively (though these values were based on adult populations).[12] Thus, in line with an approach undertaken in previous related work,[8 9 11] utility values of 1.0 (no depression) and 0.81 (depression) will be assigned to each youth based on whether their MFQ score is below or above 22, respectively, which is the cut-off for depression.

Measurement and valuation of resources and costs

Intervention resource use and costs

We will record all resources used by patients during the delivery of the intervention; these will include the time of personnel involved in the assessment of patients, delivery of education sessions, and psychotherapy, the number of medications (eg, fluoxetine, sertraline, escitalopram and duloxetine) delivered by personnel, the number of supplies and services, training of staff delivering the intervention and programme resources (eg, educational materials) related to the intervention. Subsequently, we will employ a micro-costing approach[27] to estimate the total costs associated with the delivery of the intervention (ie, we will monetise the intervention-related resource use). We will obtain the relevant unit costs for each resource from the Ontario Health Insurance Plan and the Alberta Schedule of Medical Benefits fee schedules, community mental health agencies, hospital records (to estimate the salary of professionals involved and the supplies and services) and pharmacy records, the Ontario Drug Benefit Formulary and the Alberta Pharmaceutical Information Network (to estimate the cost of medications).

Resource use

Data on health system-related resource use post-intervention for Ontario will be obtained through ICES (formerly known as the Institute for Clinical Evaluative Sciences), an independent non-profit research institute in Toronto, Ontario, which holds health records for all health services covered under the Ontario public healthcare system (eg, physician visits, emergency department visits, acute care hospitalisations, psychiatric hospitalisations). We will use a custom health service utilisation tool, developed by the research team and based on an existing tool,[28] to measure all health system-related resource use post-intervention for Alberta. This health service use tool will also be used to obtain post-intervention data on time spent to obtain care for both youths and caregivers, where applicable, for both provinces, and lost time away from work to obtain care for both youths and caregivers, where applicable, for both provinces. Trained research analysts will administer the health service utilisation tool to adolescents and caregivers at baseline and 12, 24, 36 and 52 weeks. Our data collection methods will also collect information on significant adverse events, such as psychiatric hospitalisations, episodes of self-harm with potential for high lethality and completed deaths by suicide, which will be reported if/when these instances occur.

Cost estimation

To estimate total costs, we will apply patient-level costing to value all resource use post-intervention for each adolescent (ie, direct health system costs, direct out-of-pocket costs), where the respective number of units reported (eg, number of visits, number of medications consumed) described beforehand will be multiplied by the respective unit cost.[29] The same approach will be applied to estimate time costs (eg, time spent to obtain care) and indirect costs (eg, lost work income due to appointments) for both youths and caregivers. The unit costs will be obtained from the Canadian Institute for Health Information, the Ontario Health Insurance Plan fee schedule, the Alberta Schedule of Medical Benefits and Statistics Canada, among other sources. All costs will be expressed in 2027 Canadian dollars using Statistics Canada's Consumer Price Index for Health and Personal Care.[30]

Analysis

We will compare adolescents who receive the CARIBOU-2 intervention to those who receive TAU. We will compare health outcomes and costs at baseline, 24 weeks and 52 weeks post-intervention and produce mean values (and SDs) for each treatment group. We will also produce mean differences and 95% CIs using non-parametric bootstrap regressions, which address the non-normal distribution of the cost data.[31]

We will model effectiveness and costs from baseline to 24 weeks and from baseline to 52 weeks post-intervention through the use of multivariable generalised linear mixed models, controlling for baseline covariates, such as demographics and baseline clinical measures.[32] This regression model enables researchers to assess and choose the most appropriate mean and variance functions, which is important when modelling costs given its non-normal distribution, as well as include random effects, while making use of all data available for each participant, even in the presence of missing values.[32] We will estimate separate models for each cost category (eg, physician visits, emergency department visits, acute care hospitalisations, psychiatric hospitalisations) to predict the mean cost according to the time period and treatment group. We will apply the same approach to predict mean MFQ and utility values, by time period and treatment group. We will use the statistical method of recycled predictions[33] to estimate the final predicted mean values of the MFQ scores and costs; health utility values will be used to estimate the QALYs gained using the area under the curve method.[34] These values will then be added and examined for statistical significance from baseline to 24 weeks and from baseline to 52 weeks post-intervention. The ICER,[27] the outcome of interest, will be obtained

by dividing the incremental predicted average cost and the incremental predicted average effectiveness of the two treatment groups and estimated at 24 and 52 weeks post-intervention.

Sensitivity analyses

Several sensitivity analyses will be undertaken to account for potential biases. A systematic review found that utility values reported for adolescent depression ranged from 0.495 to 0.81.[25] The main analysis will use a utility value of 0.81 for adolescents with depression; however, a deterministic one-way sensitivity analysis with a utility value of 0.495 will be undertaken to test the robustness of the results of the cost-utility analysis. As described beforehand, we will exclude participants with missing data from the main analysis; however, we will examine the sociodemographic and clinical characteristics of adolescents included in the analyses and those in the full sample to assess the impact of excluding those with missing data. In addition, we will rerun the cost-effectiveness and cost-utility analyses with imputed data on outcomes and costs using multiple imputation by chained equations.[35] We will conduct deterministic one-way sensitivity analyses to determine the robustness of our results to changes in intervention and health service unit costs in instances where precise unit costs cannot be obtained; in these cases, we will use 95% CIs to determine the range (ie, high and low-cost scenarios) to be used in the sensitivity analyses. In addition, we will compare the estimates from the multivariable generalised linear mixed model to the unadjusted mean values as well as the estimates obtained from an ordinary least squares model. We will use pattern-mixture models[36] to understand how potential outliers, and their exclusion, affect our findings as well as any deviations from distributional assumptions and the impact of baseline variables.

Uncertainty

We will estimate the multivariable generalised linear mixed models with non-parametric bootstrapping (namely 1000 bootstrap replications) to produce standard errors and p values for each incremental cost and effect, while adjusting for sampling uncertainty. We will examine uncertainty using cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs), in line with a net benefit framework.[37] Cost-effectiveness planes depict the uncertainty regarding the cost and effect estimates; this is done by plotting the respective estimated bootstrapped values.[32] CEACs provide an alternative to the ICER CIs; they are obtained from the joint distribution of incremental costs and effects from the non-parametric bootstrapping of the observed data. The CEAC shows the probability that a given intervention is cost-effective compared with the comparator for several different values that a decision-maker is hypothetically willing to pay for a unit improvement in a given health outcome.[38 39] We will calculate a series of net benefits for each individual for a range of willingness to pay values for a QALY and then compare these to $50 000 CAD, which is the cost-effectiveness threshold commonly used for decision-making in Canada.[40] We will obtain the coefficients of the differences in the net benefits between the intervention and TAU groups through bootstrapped linear regressions, which will control for the variables included in the main analysis (eg, demographics and baseline clinical measures) as well as the baseline variables of interest, such as gender, age, ethnicity and race, to account for any potential differences between the intervention and TAU groups at recruitment. We will then examine these coefficients to determine the proportion of instances in which the net benefit of the intervention group is greater than that of the TAU group for each willingness to pay value.[41] Subsequently, we will plot these proportions to obtain CEACs for each cost-effect combination. All data analyses will be undertaken using Stata V.12.

Equity

We will weight all patient outcomes equally; however, we will explore undertaking additional subgroup analyses (eg, differences by gender and ethnicity and race), where sample sizes permit, to understand whether findings differ by patient subgroups. Evidence suggests that there are gender and ethnic disparities in mental healthcare use.[42]

Approach to engaging patients and others affected by the study

The Centre for Addiction and Mental Health houses the Youth Engagement Initiative, which consists of coordinators and young people with experience in mental health services.[43] Youths from the Youth Engagement Initiative were involved in designing the content of the clinical materials, selecting outcome measurement instruments and advising on recruitment and retention strategies. Youth partners were also involved in training research analysts on data collection. In parallel, a caregiver engagement coordinator will work with caregivers with experience in the mental health systems who will provide feedback on how youth-centred care should be delivered as well as advise on caregiver recruitment into the study. Both youths and caregivers will also be involved in the interpretation and reporting of the findings.

Patient and public involvement

Patients and/or the public were not involved in the design of the economic evaluation. However, one of the authors (GL), who was involved in the drafting of the protocol, is a youth with lived experience.

ETHICS AND DISSEMINATION

Ethical approval for the larger CARIBOU-2 trial, including the economic evaluation, has been obtained from the Centre for Addiction and Mental Health as well as site-level ethics boards (019/2021; Centre for Addiction and Mental Health). All participants will provide informed consent for their data to be analysed and reported. The

results of the main trial and the economic evaluation will be submitted for publication in a peer-reviewed journal and shared with relevant policy makers across Canada.

DISCUSSION

The main objective of CARIBOU-2 is to address depression among adolescents in Canada. The results of the economic evaluation will have significant, broad and high reward impacts on several levels. As the first economic evaluation of an intervention targeting depression in Canadian youth, this study has the potential to transform how mental care for adolescents is provided in Canada. If CARIBOU-2 is found to be cost-effective, the findings of this study may help guide the allocation of healthcare resources to improve outcomes for youth and their families and shed light on the value for money of this intervention.

This work will inform whether an integrated care pathway is a cost-effective option to treat depression in adolescents. However, the proposed economic evaluations will not be without limitations. The data on resource use will be self-reported and thus subject to recall bias and potentially stigma-related under-reporting bias; however, the reliability and validity of self-reported data has been well established over recall periods comparable to those used in this study.[44–48] In addition, the study may not capture all resources used by participants (eg, a youth participant may forget to describe a visit to a school-based counsellor). Regardless, the custom data collection tool captures the most relevant health services used by this patient population. The utility values employed in this analysis plan were obtained from prior related literature as opposed to from the adolescents involved in the trial. Nonetheless, this approach has also been employed in previous economic evaluations of depression in adolescents undertaken elsewhere.[8 9 11] Finally, despite becoming increasingly common in the field of economic evaluation, this study will not characterise distributional effects,[49] that is, how impacts are distributed across different individuals or whether adjustments are made to reflect priority populations.

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Contributors CdO and DC conceived and designed the study. CdO drafted the original protocol. All authors provided comments and critical revisions on drafts of the manuscript. CdO is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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