BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-092541
Article Type:	Protocol
Date Submitted by the Author:	16-Aug-2024
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Keywords:	Adolescent, HEALTH ECONOMICS, Depression & mood disorders < PSYCHIATRY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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

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Word count

3,544

Abstract

Background: Depressive disorders in adolescents are highly prevalent and debilitating, and a risk factor for self-harm and death by suicide. In the context of recovery from the COVID-19 pandemic, strained health care resources are compounded by an increased demand for treatment services for adolescents with depression. Evidence-based treatments are available but at a cost. Therefore, identifying cost-effective strategies to optimally treat depression in adolescents is imperative. 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-randomized, cluster controlled trial.

Methods: 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 health care resource utilisation will be obtained from a mix of self-report and administrative data holdings; 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.

Discussion: This study's findings will help inform decision-making around the implementation and scale-up of an integrated care pathway for adolescent depression in Canada. Policymakers, funders, and administrators from other jurisdictions may also use these findings to inform their decisions around the provision of treatments for depression in adolescents.

Ethics and dissemination: Ethical approval for the larger CARIBOU-2 trial 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). The trial has been registered on ClinicalTrial.gov, NCT05142683. 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.

Keywords: economic evaluation, depression, adolescent, protocol, non-randomized, cluster controlled trial, integrated care pathway

Article summary

Strengths and limitations of this study

- This study will be the first economic evaluation of an intervention targeting depression in Canadian youth.
- This study will inform whether an integrated care pathway is a cost-effective option to treat depression in adolescents.
- Health service utilisation data will be self-reported and thus subject to recall bias and potentially stigma-related under-reporting bias.
- The study may not capture all health services 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.

Background

Depressive disorders in adolescents are highly prevalent and debilitating, and 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 health care resources.[5] Based on existing evidence, the cost of caring for children and youth with depression and/or anxiety in Canada is around $4 billion annually, with the most costs due to health care.[6] Without appropriate investments, the lifetime cost of a cohort of children with onset of depression and/or anxiety at the age of 10 can reach up to $1 trillion.[6] Evidence-based treatments are available but at a cost. Therefore, identifying cost-effective solutions to treat depression in adolescents is imperative. Furthermore, 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 treatment for adolescent depression, particularly within Canada.

Review of existing economic evidence

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.[7] We found few economic evaluations (n=10), with the majority having been undertaken either in the UK (n=4) or the USA (n=4). Most studies undertook an economic evaluation alongside a clinical trial (n=9), whereas only one study undertook a modeling-based economic evaluation. Of these, four were undertaken alongside trials testing cognitive behavioural therapy (CBT) alone or CBT and selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, in combination.[7] One study examined the economic evaluation of a trial of a collaborative care model,[8] 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,[9] while another examined an exercise program.[10] Five of the ten studies adopted the societal perspective, where all relevant costs, regardless the payer, and opportunity costs were considered. Nine of the ten studies examined quality-adjusted life-years (QALYs) as the main outcome of the economic evaluation. Few studies (n=2) undertook equity/sub-group analyses. CBT with and without SSRIs were found to be cost-effective relative to treatment as usual in three studies.[7] The collaborative care model, compared to treatment as usual, was also found to be cost-effective. In other cases where individual or combined treatment options were compared to active structured treatments, findings were mixed.[7] Overall, the scoping review found few studies examining cost-effectiveness of multi-component 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, inclusion of the major long-term and/or negative outcomes regarding the primary outcome measure(s), and engagement with patients and others affected by the study, among others.[7]

Objective

The objective of this study protocol is to delineate the economic evaluation of the CARIBOU-2 intervention within the context of a non-randomized, cluster controlled clinical trial, while building on prior related work. It is hypothesised that the CARIBOU-2 intervention will be cost-

effective in the treatment of depressive symptoms in help-seeking adolescents compared to treatment as usual over a 52-week period.

Methods

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.[11] 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 1st line treatment is CBT and 2nd line treatment is a brief psychosocial intervention);[9] 4) caregiver support; 5) medication options (where 1st line of treatment is fluoxetine, 2nd line is sertraline, 3rd line is escitalopram, and 4th 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.[12] 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.[12] The comparator, treatment as usual (TAU), may or may not involve any of the following: assessment, psychoeducation, psychotherapy, medication, and family work. 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.[13] 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 are assigned to the CARIBOU intervention. See the primary study protocol for further details.[14]

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 the Canadian Agency for Drugs and Technologies in Health (CADTH)[15] 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).[17] The second economic evaluation of CARIBOU-2 will be a cost-utility analysis (i.e., a cost-effectiveness analysis where effectiveness is measured using a utility measure), in line with the CADTH guidelines for the recommended reference case analysis,[15] 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. Both economic evaluations will be undertaken at two time points, 24 and 52 weeks post-enrollment 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).

Study population

Participant recruitment (planned n=300) will occur over 4.5 years, from February 2022 to September 2027, at 4 to 6 sites (hospitals and community-based mental health agencies) across southern Ontario and Alberta, where youth often receive outpatient mental health care. Adolescents will self-refer or be referred by a third party (e.g., doctors, school counselors, caregivers) to the site, and then recruited after their intake. Site staff (e.g., intake workers, clinicians) will assess the youth, including the use of the MFQ[17] 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 13 and 18 years old, 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 (e.g., 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, imminent risk of suicide requiring hospitalisation as per judgment of the assessing clinician, and those unable to provide informed consent to the study for any reason.

If the adolescent agrees, caregivers will be also asked to participate in the study. In addition, supervisors and clinicians interested in participating will be recruited for the study. Other than fluency in English, and capacity to make decisions regarding consenting to research, there are no inclusion or exclusion criteria for caregiver or supervisor/clinician participation.

TAU will be provided in the same hospital/community mental health agency and may or 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 health care payer (i.e., the Ontario Ministries of Health and Long-term Care and the Alberta Ministry of Health), in line with the CADTH guidelines for the recommended reference case analysis.[15] According to the CADTH 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. Therefore, we will also undertake an additional analysis (i.e., 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.

Time horizon and discounting

The time horizon of the analysis will be 52 weeks post-enrollment, 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 one year, discounting is not needed.

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 assesses depressive symptomatology in children and adolescents between the ages 8 and 18.[17] The questionnaire consists of several descriptive phrases on how the adolescent has been feeling or acting over the prior two 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 two weeks. The MFQ score ranges from 0 to 66, where cases with a score of 22 or more are suggestive of likely depression.[18]

The outcome of the cost-utility 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[19] found that utility values reported for depression in this population ranged from 0.495[20] to 0.81.[21] 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).[8] Thus, in line with in previous related work,[22-24] 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, the cut-off for depression. In addition, we will explore the possibility of using utility values of 0.8 and 0.6 for mild depression (for MFQ scores between 22 and 42) and moderate to severe depression (for MFQ scores of 43 and above), respectively, based on prior work[25] and as done elsewhere.[8]

Measurement and valuation of resources and costs

Intervention resource use and costs

We will employ a micro-costing approach[26] to estimate all costs associated with delivering the intervention: costs of personnel delivering CARIBOU-2 (e.g., assessment, delivery of education sessions, psychotherapy), medication (e.g., fluoxetine, sertraline, escitalopram, and duloxetine), supplies and services, training, and program resources (e.g., educational materials). We will obtain unit costs for each resource from the Ontario Health Insurance Plan fee schedule, community mental health agencies, and hospital records to estimate the salary of professional involved and the supplies and services, and from pharmacy records and the Ontario Drug Benefit formulary to estimate the cost of medications.

Health services utilisation

We will use a custom health service utilisation tool, developed by the research team and based on an existing tool,[27] to measure direct out-of-pocket costs to patients and caregivers (e.g., travel costs), direct caregiver time costs, and caregiver indirect costs (e.g., caregivers' lost income due to appointments). Trained research analysts will administer the health service utilisation tool to youth and caregivers at baseline, 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. Additional data regarding direct costs to the health care system (for Ontario only) 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 administrative health care data (including unit costs) for all health services covered under the public health care system (e.g., physician visits, emergency departments visits, hospitalisations).

Health care costs

We will apply patient-level costing to value the health care services used by each adolescent during the CARIBOU-2 trial, where the number of units reported will be multiplied by the respective unit cost.[28] We will use unit costs provided by the Canadian Institute for Health Information, the Ontario Health Insurance Plan fee schedule, and the Alberta Schedule of Medical Benefits, among other sources. Health care costs will be expressed in 2027 Canadian dollars using Statistics Canada's Consumer Price Index for Health and Personal Care.[29]

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 standard deviations) for each treatment group. We will also produce mean differences and 95% confidence intervals using non-parametric bootstrap regressions, which address the non-normal distribution of the cost data.[30]

We will model effectiveness and costs from baseline to 24 weeks and from baseline to 52 weeks post-intervention through the use of multivariable generalized linear mixed models, controlling for baseline covariates, such as demographics and baseline clinical measures.[31] 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. We will estimate separate models for each cost category 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 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. 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 incremental cost-effectiveness ratio (ICER), the outcome of interest, will be obtained by dividing the incremental predicted cost and the incremental predicted effectiveness of the two treatment groups.

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. 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 re-run the cost-effectiveness and cost-utility analyses with imputed data on outcomes and costs using multiple imputation by chained equations. We will conduct a deterministic one-way sensitivity analysis to determine the robustness of our results to changes in intervention and health service unit costs; we will use 95% confidence intervals to determine the range used in the sensitivity analyses. In addition, we will compare the estimates from the multivariable generalized linear mixed model to the unadjusted mean values as well as the estimates obtained from an ordinary least squares model. Finally, we will use pattern-mixture models to understand how potential outliers affect our findings as well as any deviations from distributional assumptions and the impact of baseline variables.

Uncertainty

We will estimate the multivariable generalized linear mixed models with nonparametric bootstrapping (namely, 1,000 bootstrap replications) to produce standard errors and p-values for each incremental cost and incremental effect, while adjusting for sampling uncertainty. Again, we will undertake deterministic one-way sensitivity analyses to understand the level of confidence of the ICERs produced. We will examine uncertainty using cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs), in line with a net benefit framework.[32] Cost-effectiveness planes depict the uncertainty regarding the costs and effect estimates; this is done by plotting the respective estimated bootstrapped values.[31] CEACs provide an alternative to the ICER confidence intervals; they are obtained from the joint distribution of incremental costs and effects from the nonparametric bootstrapping of the observed data. The CEAC shows the probability that a given intervention is cost-effective compared to the comparator, for several different values that a decision-maker is hypothetically willing to pay for a unit improvement in a given health outcome.[33,34] 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.[35] 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 (e.g., demographics and baseline clinical measures) as well as the baseline variable of interest. 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.[36] Subsequently, we will plot these proportions to obtain CEACs for each cost-effect combination. All data analyses will be undertaken using Stata, version 12.

Equity

We will weight all patient outcomes equally; however, we will explore undertaking subgroup analyses related to heterogeneity due to clinical severity, where possible. Furthermore, we will explore undertaking additional sub-group analyses (e.g., differences by gender and ethnicity/race), where sample size permit.

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.[37] The

Youth Engagement Initiative has been 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 guide caregivers with relevant experience in the mental health systems in providing relevant feedback as it pertains to caregivers. Both youth and caregivers will also be involved in the interpretation and reporting of the findings.

How the economic evaluation will support evidence-based decision making in Canada

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. This study has the potential to transform how mental care for adolescents is provided in Canada as well as in other similar, high-income countries. The findings of this study will help inform the allocation of health care resources to improve outcomes for youth and their families as well as inform the value for money of this intervention. Moreover, the economic evaluation of CARIBOU-2 will help inform the dissemination and scale up of an evidence-based youth intervention in Canada.

Strengths and limitations

This study will be the first economic evaluation of an intervention targeting depression in Canadian youth and will represent a methodological improvement over previous related studies. This work will also inform whether an integrated care pathway is a cost-effective option to treat depression in adolescents. However, the economic evaluations will not be without limitations. The data on health service utilisation 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.[38-42] In addition, the study may not capture all health services used by participants (e.g., a youth participant may forget to describe a visit to a school-based counselor). 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.[22-24] Finally, despite becoming increasingly common in the field of economic evaluation, this study will not characterise distributional effects.[43]

Author contributions
CdO and DBC conceived and designed the study. CdO drafted the original protocol. All authors provided comments and critical revisions on drafts of the manuscript.

Source of funding
This study was funded by the Canadian Institutes of Health Research and the Cundill Centre for Child and Youth Depression. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. No endorsement by the funders is intended or should be inferred.

Competing interests
The authors do not report any conflicts of interest in accordance with the International Committee of Medical Journal Editors requirements.

Patient and public involvement
Patients and/or the public were involved in the design of the economic evaluation.

Acknowledgements
None

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BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-092541.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Feb-2025
Complete List of Authors:	de Oliveira, Claire; Centre for Addiction and Mental Health; University of Toronto, Institute of Health Policy, Management and Evaluation Mason, Joyce; Centre for Addiction and Mental Health Amani, Bahar; Centre for Addiction and Mental Health Liddell, Gray; Centre for Addiction and Mental Health Szatmari, Peter; Centre for Addiction and Mental Health; University of Toronto, Department of Psychiatry Henderson, Jo; Centre for Addiction and Mental Health; University of Toronto, Department of Psychiatry Courtney, Darren; Centre for Addiction and Mental Health, Psychiatry; University of Toronto, Psychiatry
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Mental health
Keywords:	Adolescent, HEALTH ECONOMICS, Depression & mood disorders < PSYCHIATRY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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

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Word count

3,826

Abstract

Introduction: Depressive disorders in adolescents are highly prevalent and debilitating, and a risk factor for self-harm and death by suicide. In the context of recovery from the COVID-19 pandemic, strained health care resources are compounded by an increased demand for treatment services for adolescents with depression. Therefore, identifying cost-effective strategies to optimally treat depression in adolescents is imperative. 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-randomized, 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 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: The CARIBOU-2 trial has been registered on ClinicalTrial.gov, NCT05142683.

Keywords: economic evaluation, depression, adolescent, protocol, non-randomized, cluster controlled trial, integrated care pathway

Article summary

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 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 health care resources.[5] Research also suggests that the economic burden of depression is increasing among individuals between the ages of 18 and 34 years old.[6] Therefore, identifying cost-effective solutions to treat depression in adolescents is imperative. Furthermore, 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.[7] We found few economic evaluations (n=10), with the majority having been undertaken either in the UK (n=4) or the USA (n=4). Most studies undertook an economic evaluation alongside a clinical trial (n=9), whereas only one study undertook a modeling-based economic evaluation. Of these, four were undertaken alongside trials testing cognitive behavioural therapy (CBT) alone or CBT and selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, in combination.[7] One study examined the economic evaluation of a trial of a collaborative care model,[8] 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,[9] while another examined an exercise program.[10] Five of the ten studies adopted the societal perspective, where all relevant costs, regardless the payer, and opportunity costs were considered. Nine of the ten studies examined quality-adjusted life-years (QALYs) as the main outcome of the economic evaluation. Few studies (n=2) undertook equity/sub-group analyses. CBT with and without SSRIs were found to be cost-effective relative to treatment as usual in three studies.[7] The collaborative care model, compared to treatment as usual, was also found to be cost-effective.[7] In other cases where individual or combined treatment options were compared to active structured treatments, findings were mixed.[7] Overall, the scoping review found few studies examining cost-effectiveness of multi-component 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, among others.[7]

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-randomized, cluster controlled clinical trial, while building on prior related work. It is hypothesised that the CARIBOU-2 intervention will be cost-effective (i.e., more costly but more effective) in the treatment of depressive symptoms in help-seeking adolescents compared to treatment as usual 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.[11] 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 1st line treatment is CBT and 2nd line treatment is a brief psychosocial intervention);[9] 4) caregiver support; 5) medication options (where 1st line of treatment is fluoxetine, 2nd line is sertraline, 3rd line is escitalopram, and 4th 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.[12] 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.[12] The comparator, treatment as usual (TAU), may or may not involve any of the following: assessment, psychoeducation, psychotherapy, medication, and family work.[12] 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 USA 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.[13] 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. See the primary study protocol for further details.[14]

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,[15] 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),[17] where the MFQ measures depressive symptoms. The second economic evaluation of CARIBOU-2 will be a cost-utility analysis (i.e., a cost-effectiveness analysis where effectiveness is measured using a utility measure), in line with the CDA guidelines for the recommended reference case analysis,[15] 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.[15] Both economic evaluations will be undertaken at two time points, 24 and 52 weeks post-enrollment 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 4 to 6 sites (hospitals and community-based mental health agencies) across southern Ontario and Alberta, where youth often receive outpatient mental health care. Adolescents will self-refer or be referred by a third party (e.g., doctors, school counselors, caregivers) to the site, and then recruited after their intake. Site staff (e.g., intake workers, clinicians) will assess the youth, including the use of the MFQ[17] 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 13 and 18 years old, 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 (e.g., 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, imminent risk of suicide requiring hospitalisation as per judgment of the assessing clinician, and those unable to provide informed consent to the study for any reason.

If the adolescent agrees, caregivers will be also asked to participate in the study. In addition, supervisors and clinicians interested in participating (e.g., providing care to adolescents) will be recruited for the study. Clinicians must be social workers, social service workers, occupational therapists, nurses, psychologists, psychiatrists, or registered therapists to deliver the interventions. Other than fluency in English, and capacity to make decisions regarding consenting to research, there are no inclusion or exclusion criteria for caregiver or supervisor/clinician participation.

TAU will be provided in the same hospital/community mental health agency and may or 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 health care payer (i.e., 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.[15] 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.[15] Therefore, we will also undertake an additional analysis (i.e., 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.

Time horizon and discounting

The time horizon of the analysis will be 52 weeks post-enrollment, 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 one year, discounting is not needed.[15]

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 assesses depressive symptomatology in children and adolescents between the ages 8 and 18.[17] The questionnaire consists of several descriptive phrases on how the adolescent has been feeling or acting over the prior two 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 two weeks. The MFQ score ranges from 0 to 66, where cases with a score of 22 or more are suggestive of likely depression.[18]

The outcome of the cost-utility 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[19] found that utility values reported for depression in this population ranged from 0.495[20] to 0.81.[21] 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).[8] Thus, in line with an approach undertaken in previous related work,[22-24] 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. In addition, we will explore the possibility of using utility values of 0.8 for mild depression (i.e., for MFQ scores between 22 and 42) and 0.6 for moderate to severe depression (i.e., for MFQ scores of 43 and above), based on prior work[25] and as done elsewhere.[8]

Measurement and valuation of resources and costs

Intervention resource use and costs

We will employ a micro-costing approach[26] to estimate all costs associated with delivering the intervention: costs of personnel providing CARIBOU-2 (e.g., assessment, delivery of education sessions, psychotherapy), medication (e.g., fluoxetine, sertraline, escitalopram, and duloxetine) and its delivery by personnel, supplies and services, training, and program resources (e.g., educational materials). We will obtain 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 (for Ontario only) 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 public health care system (e.g., physician visits, emergency departments visits, acute care hospitalisations, psychiatric hospitalisations). In addition, we will use a custom health

service utilisation tool, developed by the research team, and based on an existing tool,[27] to measure all health system-related resource use (for Alberta only), 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, 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.

Costs

We will apply patient-level costing to value all resources used by each adolescent (i.e., direct health system, direct out-of-pocket costs), where the respective number of units reported (e.g., number of visits, number of medications consumed) will be multiplied by the respective unit cost.[28] The same approach will be applied to estimate time costs (e.g., time spent to obtain care) and indirect costs (e.g., lost work income due to appointments). Costs of adverse events (e.g., episodes of self-harm) will also be costed. 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. Health care costs will be expressed in 2027 Canadian dollars using Statistics Canada's Consumer Price Index for Health and Personal Care.[29]

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 standard deviations) for each treatment group. We will also produce mean differences and 95% confidence intervals using non-parametric bootstrap regressions, which address the non-normal distribution of the cost data.[30]

We will model effectiveness and costs from baseline to 24 weeks and from baseline to 52 weeks post-intervention through the use of multivariable generalized linear mixed models, controlling for baseline covariates, such as demographics and baseline clinical measures.[31] 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.[31] We will estimate separate models for each cost category 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[32] 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.[33] 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 incremental cost-effectiveness ratio (ICER), 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.[19] 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 re-run the cost-effectiveness and cost-utility analyses with imputed data on outcomes and costs using multiple imputation by chained equations.[34] 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% confidence intervals to determine the range to be used in the sensitivity analyses. In addition, we will compare the estimates from the multivariable generalized 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[35] 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. Finally, we will undertake deterministic one-way sensitivity analyses to understand the level of confidence of the ICERs produced.

Uncertainty

We will estimate the multivariable generalized linear mixed models with nonparametric bootstrapping (namely, 1,000 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.[36] Cost-effectiveness planes depict the uncertainty regarding the costs and effect estimates; this is done by plotting the respective estimated bootstrapped values.[31] CEACs provide an alternative to the ICER confidence intervals; they are obtained from the joint distribution of incremental costs and effects from the nonparametric bootstrapping of the observed data. The CEAC shows the probability that a given intervention is cost-effective compared to the comparator, for several different values that a decision-maker is hypothetically willing to pay for a unit improvement in a given health outcome.[37,38] 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.[39] 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 (e.g., 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 treatment as usual 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.[40] Subsequently, we will plot these proportions to obtain CEACs for each cost-effect combination. All data analyses will be undertaken using Stata, version 12.

Equity

We will weight all patient outcomes equally; however, we will explore undertaking subgroup analyses related to heterogeneity due to clinical severity, where possible. Furthermore, we will explore undertaking additional sub-group analyses (e.g., differences by gender and ethnicity and race), where sample sizes permit, to understand whether findings differ by patient sub-groups.

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.[41] 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 (G. Liddell), 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 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.

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 health care resources to improve outcomes for youth and their families, shed light on the value for money of this intervention, and help inform the dissemination and scale up of an evidence-based youth intervention in Canada.

This work will inform whether an integrated care pathway is a cost-effective option to treat depression in adolescents. This study will also represent a methodological improvement over previous related studies. 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.[42-46] In addition, the study may not capture all resources used by participants (e.g., a youth

participant may forget to describe a visit to a school-based counselor). 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.[22-24] Finally, despite becoming increasingly common in the field of economic evaluation, this study will not characterise distributional effects,[47] i.e., how impacts are distributed across different individuals or whether adjustments are made to reflect priority populations.

Contributors

CdO and DBC 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.

Funding

This study was funded by the Canadian Institutes of Health Research and the Cundill Centre for Child and Youth Depression. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. No endorsement by the funders is intended or should be inferred.

Competing interests

The authors do not report any conflicts of interest in accordance with the International Committee of Medical Journal Editors requirements.

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BMJ Open

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

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-092541.R2
Article Type:	Protocol
Date Submitted by the Author:	15-Apr-2025
Complete List of Authors:	de Oliveira, Claire; Centre for Addiction and Mental Health; University of Toronto, Institute of Health Policy, Management and Evaluation Mason, Joyce; Centre for Addiction and Mental Health Amani, Bahar; Centre for Addiction and Mental Health Liddell, Gray; Centre for Addiction and Mental Health Szatmari, Peter; Centre for Addiction and Mental Health; University of Toronto, Department of Psychiatry Henderson, Jo; Centre for Addiction and Mental Health; University of Toronto, Department of Psychiatry Courtney, Darren; Centre for Addiction and Mental Health, Psychiatry; University of Toronto, Psychiatry
Primary Subject Heading:	Health economics
Secondary Subject Heading:	Mental health
Keywords:	Adolescent, HEALTH ECONOMICS, Depression & mood disorders < PSYCHIATRY, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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

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Word count
3,941

Abstract

Introduction: Depressive disorders in adolescents are highly prevalent and debilitating, and a risk factor for self-harm and death by suicide. In the context of recovery from the COVID-19 pandemic, strained health care 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-randomized, 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: The CARIBOU-2 trial has been registered on ClinicalTrial.gov, NCT05142683.

Keywords: economic evaluation, depression, adolescent, protocol, non-randomized, cluster controlled trial, integrated care pathway

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 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 health care 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 modeling-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 program.[14] Five of the ten studies adopted the societal perspective, where all relevant costs, regardless the payer, and opportunity costs were considered. Nine of the ten studies examined quality-adjusted life-years (QALYs) as the main outcome of the economic evaluation. Few studies (n=2) undertook equity/sub-group 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 were found to be cost-effective relative to treatment as usual 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 (DALYs) between $9,000-$34,000 in another.[10] The collaborative care model, compared to treatment as usual, 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 to 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 US found an ICER per QALY of -$28,833.[9] Overall, the scoping review found few studies examining cost-effectiveness of multi-component 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-randomized, cluster controlled clinical trial, while building on prior related work. It is hypothesised that the CARIBOU-2 intervention will be cost-

effective (i.e., specifically more costly but more effective) in the treatment of depressive symptoms in help-seeking adolescents compared to treatment as usual 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 1st line treatment is CBT and 2nd line treatment is a brief psychosocial intervention);[9] 4) caregiver support; 5) medication options (where 1st line of treatment is fluoxetine, 2nd line is sertraline, 3rd line is escitalopram, and 4th 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, treatment as usual (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 USA 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 (CHEERS) 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 (i.e., 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-enrollment 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 4 to 6 sites (hospitals and community-based mental health agencies) across southern Ontario and Alberta, where youth often receive outpatient mental health care. Adolescents will self-refer or be referred by a third party (e.g., doctors, school counselors, caregivers) to the site, and then recruited after their intake. Site staff (e.g., 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 13 and 18 years old, 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 (e.g., 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, imminent risk of suicide requiring hospitalisation as per judgment of the assessing clinician, and those unable to provide informed consent to the study for any reason.

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

TAU will be provided in the same hospital/community mental health agency and may or 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 health care payer (i.e., 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 (i.e., 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 health care system (i.e., 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-enrollment, 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 one 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 8 and 18.[23] The questionnaire consists of several descriptive phrases on how the adolescent has been feeling or acting over the prior two 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 two 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 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 (e.g., fluoxetine, sertraline, escitalopram, and duloxetine) delivered by personnel, the number of supplies and services, training of staff delivering the intervention, and program resources (e.g., 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 (i.e., 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 health care system (e.g., physician visits, emergency departments 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, 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 (i.e., direct health system, direct out-of-pocket costs), where the respective number of units reported (e.g., 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 (e.g., time spent to obtain care) and indirect costs (e.g., lost work income due to appointments) for both youth 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 standard deviations) for each treatment group. We will also produce mean differences and 95% confidence intervals 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 generalized 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 (e.g.,

physician visits, emergency departments 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 incremental cost-effectiveness ratio (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 re-run 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% confidence intervals to determine the range (i.e., high- and low-cost scenarios) to be used in the sensitivity analyses. In addition, we will compare the estimates from the multivariable generalized 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 generalized linear mixed models with nonparametric bootstrapping (namely, 1,000 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 confidence intervals; they are obtained from the joint distribution of incremental costs and effects from the nonparametric bootstrapping of the observed data. The CEAC shows the probability that a given intervention is cost-effective compared to 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 (e.g., 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 treatment as usual 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, version 12.

Equity

We will weight all patient outcomes equally; however, we will explore undertaking additional sub-group analyses (e.g., differences by gender and ethnicity and race), where sample sizes permit, to understand whether findings differ by patient sub-groups. Evidence suggests that there are gender and ethnic disparities in mental health care 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 (G. Liddell), 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 health care 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 (e.g., a youth participant may forget to describe a visit to a school-based counselor). 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] i.e., how impacts are distributed across different individuals or whether adjustments are made to reflect priority populations.

Contributors

CdO and DBC 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.

Funding

This study was funded by the Canadian Institutes of Health Research and the Cundill Centre for Child and Youth Depression. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. No endorsement by the funders is intended or should be inferred.

Competing interests

The authors do not report any conflicts of interest in accordance with the International Committee of Medical Journal Editors requirements.

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