Cost-Effectiveness of Integrative Concepts for the Treatment of Oncologcial Patients (OCEANic): Protocol for a Systematic Review [1a]

Contact [3a]

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Registration [2]

In accordance with the guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on 25 March 2025 and was last updated on 10 April, 2025 (registration number 1019386) (1). The study protocol is written in line with PRISMA-P 2015 statement (2).

Abstract

Background: Integrative oncology combines conventional cancer treatments with complementary medicine to enhance patient-centered care, symptom management, and overall well-being. Despite growing demand in Europe, challenges such as unequal access, reimbursement policies, and limited cost-effectiveness research hinder its broader integration into healthcare systems. This systematic review will evaluate the financial sustainability of integrative oncology interventions, providing evidence to support policy decisions and future investments in patient-centered cancer care.

Methods: A systematic review will be conducted following PRISMA guidelines, applying PICO criteria for study inclusion, focusing on adult cancer patients receiving integrative therapies and evaluating their economic impact. The review is currently in the literature search phase, using predefined search terms across selected databases. Studies published in peer-reviewed journals, including randomized and non-randomized trials, will be considered, while studies on adolescents or without economic evaluations will be excluded. Records will be managed using EndNote, and two independent reviewers will assess study eligibility through title and abstract screening, resolving discrepancies through discussion, with a third reviewer if needed. Data will be extracted independently using a standardized form, including study characteristics, sample size, outcomes, and cost-effectiveness details. Comparative analyses will focus on clinical and humanistic outcomes, using key metrics like ICER and CBR. A narrative synthesis will evaluate study quality and methodology, with no meta-analysis due to expected heterogeneity. As this study does not involve human participants or personal data, ethics approval is not required.

Results: The systematic review is currently in progress. Pilot work and initial study identification have begun, though not yet completed. Screening of search results is scheduled to commence in mid-May 2025, followed by data extraction in early June. Completion of the review is anticipated by the end of October 2025.

Discussion: The findings will provide valuable insights into the cost-effectiveness of integrative oncology interventions, informing healthcare policy, clinical practice, and future research directions. By identifying financially sustainable integrative treatments, this project aims to enhance patient care and optimize resource allocation within oncology healthcare systems.

Trial registration: PROSPERO, registration number 1019386, date of registration 25 March, 2025.

Contributions [3b]

EB, HB, HS, FS, and GS provided funding searches. AT drafted the manuscript. TR contributed to the health economic issues. All authors contributed to the development of the selection criteria, the risk of bias assessment strategy and data extraction criteria. AT, SLO developed the search strategy and provided statistical expertise. All authors reviewed the search strategy and gave approval. All authors read, provided feedback and approved the final manuscript.

Amendment [4b]

The current protocol version is version 1.0, dated from 25 March 2025. Important protocol amendments post registration will be recorded and included in dissemination.

Sponsor/Funder [5b]

This study is being conducted by the EUROCAM, the Charité Competence Center for Traditional and Integrative Medicine (CCCTIM) Charité – Universitätsmedizin Berlin, the Research Institute Havelhöhe at the hospital Havelhöhe (FIH), the IVAA, and the Institute for Social Medicine, Epidemiology and Health Economics Charité. The IVAA, the CCCTIM and the FIH are the sponsors of the systematic review.

The International Federation of Anthroposophic Medical Associations (IVAA), the Weleda AG, the Iscador AG, the Abnoba GmbH, the Helixor Heilmittel GmbH, the Holistic Medicine Network in Berlin, the Lukas GmbH, Labo-Life, and Alpen Pharma GmbH funded this research.

Role of sponsor/funder [5c]

The sponsor is non-commercial. The sponsor ensures quality management, qualified and trained personnel, protocol compliance, and timely procurement of the systematic review, supports the systematic review with personnel resources, and is involved in the development of the systematic review strategy, methodology and project development. The funders has no role in the development of the protocol or of the systematic review.

Introduction

Rationale [6]

Integrative oncology (IO) is defined as "*Integrative oncology is a patient-centered, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions alongside conventional cancer treatments*" (3). IO is gaining recognition for improving patient-centered care, addressing quality of life, symptom management, and overall well-being. In Europe, there is increasing interest and demand from citizens for integrative oncology services, as well as successful examples of meaningful integration of conventional medicine with Traditional, Complementary, and Integrative Healthcare (TCIH). However, access to TCIH practitioners, the availability of medicinal products, and reimbursement policies remain uneven. These challenges hinder the fulfillment of patients' rights to choose their preferred healthcare approaches. Cost-effectiveness in this field remains underexplored, making it challenging to determine their

financial sustainability and feasibility within healthcare systems. Assessing the cost-effectiveness of integrative oncology is particularly relevant given the financial constraints faced by healthcare systems across Europe.

Systematic reviews in the field of integrative oncology are rare. An economic evaluation by Huebner et al. emphasized the challenges in conducting economic evaluations of complementary and alternative medicine in oncology (5). The authors pointed out difficulties in defining effectiveness parameters and selecting appropriate comparative treatments. They recommended a comprehensive assessment approach that incorporates both direct and indirect costs, tailored to the holistic nature of complementary and alternative therapies. In summary, while existing literature indicates that integrative oncology may offer cost-effective benefits, the cumulative evidence is limited and varies in quality. Further rigorous economic evaluations are necessary to draw definitive conclusions about the cost-effectiveness of integrative approaches in cancer care. Most systematic reviews on the cost-effectiveness of integrative medicine tend to focus on broader populations rather than specifically on oncological patients. For instance, a comprehensive systematic review by Herman et al. analyzed 338 economic evaluations of complementary and integrative medicine up to 2010 (4). Among the 114 full economic evaluations published between 2001 and 2010, 27% met high-quality criteria, and 29% of these demonstrated health improvements alongside cost savings compared to usual care. However, the authors noted significant variation in the overall quality of these studies and recommended more rigorous research to support these findings. Additionally, a systematic review currently registered in 2024 in the PROSPERO registry is still ongoing and has yet to be finalized. While it encompasses all types of complementary, alternative, traditional, and conventional medicine, it does not focus on oncological patients and specifically evaluates the economics of these therapies in low- and middle-income countries (11).

Objective [7]

This study protocol describes a systematic review that assesses cost-effectiveness of integrative oncology care. The systematic review will identify key cost drivers, evaluate methodologies used in cost-effectiveness analyses, and explore the feasibility of integrating complementary and alternative treatments into conventional oncology care. The findings will support evidence-based decision-making for policymakers, healthcare providers, and researchers, guiding future investments in patient-centered cancer care and promoting the adoption of integrative oncology at European, national, and regional levels.

METHODS

A systematic review will be conducted in accordance with the PRISMA guidelines to ensure a rigorous and transparent methodology (2)]. Eligibility criteria according to PICO framework (Population, Intervention, Comparison, Outcome) will be applied (6). A 17-item checklist in accordance with Moher et al. has been included as supplementary table S1.

Eligibility criteria [8]

Inclusion criteria

Only studies published in peer-reviewed journals will be considered. The systematic review will include randomized controlled as well as non-randomized studies. **Population**: Single studies involving data of adults diagnosed with oncological primary disease will be included. **Intervention**: Eligible studies must involve data on cancer patients receiving integrative therapies. Studies in which a comparison between at least two groups has been performed and one of these groups has received integrative oncological treatment (search terms for integrative oncology can be found in chapter "Search strategy"). Pre-clinical studies will be excluded**. Comparison:** Studies will be included in which at least one integrative oncology concept is compared to at least one conventional, standard-oncological or guideline-oriented oncological concept (which may include watch-and wait strategies as well). **Outcome:** This review will include studies that evaluate the cost-effectiveness, cost-benefit, cost-utility, or economic impact of integrative oncology interventions. **Perspective:** The systematic review must use at least one recognized perspective—for example, society, third-party payer, hospital or employer.

Exclusion criteria

Studies that do not include an economic evaluation component, as well as abstracts, conference proceedings, and non-peer-reviewed sources, will be excluded. Additionally, studies that focus on integrative medicine but are not related to cancer care will not be considered for inclusion.

Information Sources [9]

The search will employ a comprehensive and sensitive topic-based strategies designed for each database from inception to 7 April, 2025. There will be no language or geographical restrictions. Databases include CINAHL – Cumulative Index to Nursing and Allied Health Literature, EconLit, and EMBASE vis Ovid, PsycInfo, and PubMed.

Search strategy [10]

The search will incorporate Boolean search strings using key terms related to integrative oncology, health economic evaluation, and oncology treatment models, see search strategy, table 1. Other studies will be identified by contacting authors or experts, looking through all the articles that cite the papers included in reviews and searching trial or study registers. Only published studies will be sought. There are no language and no data restrictions. The search will be performed by two independent researchers.

Table 1.
Boolean search strategy; advanced search 08.04.2025

1	Integrative OR integrated OR complementary OR alternative OR holistic OR traditional OR whole person OR whole system OR non-pharmacol* OR supportive OR herb* OR plant* OR mistletoe OR add-on OR concomitant OR viscum OR supplement* OR ayurved* OR chines* OR anthropos* OR TCM OR Asian OR oriental OR homeopath* OR globul* OR taiji OR tai ji OR tai-chi OR tai chi OR qigong OR qi gong OR chikung OR chi kung OR exercise OR physical OR mind-body OR relax* OR breathing OR mindful OR rehabil* OR yangsheng OR yang sheng OR	4,775,163

	nurs* OR counselling OR counseling OR electro* OR supervision OR nutrition OR music OR art OR yoga OR behavi* OR mental OR psycho* OR spiritual OR vitamin OR botanic* OR phyto* OR ginger OR garlic OR neem OR green tea OR turmeric OR berberine OR astragalus OR ginseng OR mushroom OR Echinacea OR manuka honey OR clove OR acupunct* OR acupress* OR neural therap* OR dry needl* OR stress OR anxiety OR distress OR fatigue OR pain OR hypno* OR palliat* OR depression OR nausea OR xerostomia OR healing OR bioenergy OR reiki therapy OR touch OR helleborus OR quality of life OR massage OR eurythm* OR surviv* OR remission OR recovery OR efficacy OR safety OR efficiency	
2	cost-eff* OR cost eff* OR cost of illness OR cost benefit analysis OR cost utility analysis OR health care cost OR finance* OR health care financing OR economic evaluation OR economic aspect OR economic health economics OR cost minimization analysis OR direct cost indirect cost OR out-of-pocket cost OR health expenditure OR budget impact analysis OR financial burden OR reimbursement OR payment model OR insurance coverage OR cost saving OR value-based care return on investment OR economic impact OR pharmacoeconomic economic modeling OR health economic model OR resource allocation cost allocation OR economic outcome	68,015
3	onco* OR cancer* OR neoplas* OR metasta* OR carcino* OR malign* tumor* OR tumour* OR lymphom* OR leukem* OR sarcom*	4,169,440
4	1 AND 2 AND 3	7,955

Study records

Data management [11a]

Records will be managed through End Note, a specific software for managing bibliographies.

Selection process [11b]

Two independent reviewers (AT and SLO) will independently search information sources and screen titles and abstracts to assess study eligibility. Each eligibility criterion will be graded as *eligible*, *not eligible*, or *might be eligible* (7). Studies will be considered potentially relevant when they cannot be clearly excluded based on their title and abstract alone (8), following discussion between the two reviewers. Full texts will be obtained for abstracts lacking sufficient information or where there is disagreement. Both reviewers will then independently assess the full text to determine final inclusion based on predefined criteria. Exclusion reasons will be recorded in a standardized data extraction excel-based form. The reviewers will compare their assessments, resolving discrepancies through discussion. In the event of disagreement, a third reviewer (FS) will assist in the final decision (9).

Data collection process [11c]

Data will be extracted independently by at least two reviewers (AT/SLO) with a process to resolve differences (8). Authors will be asked to provide any required data not available in published reports. Data will be checked for consistency and clarity. The standardized form will be used to collect information on study characteristics, including study design, year of publication, location, sample size, cancer type, integrative oncology care type, economic-effectiveness evaluation type and cost perspective.

Data items [12]

Data extracted will include the following summary data: study design, sample characteristics, sample size, outcomes, and timescales to reflect disorder state, acute, subacute and chronic, outcomes.

Outcomes and prioritization [13]

Comparative analyses will evaluate both costs and outcomes, including clinical and humanistic impacts. Key measures such as the incremental cost-effectiveness ratio, cost-benefit-ratio, and other metrics that compare costs with clinical outcomes, will be included to assess the value of interventions.

Risk of bias in individual studies [14]

Risk of bias for each included trial will be independently assessed by two independent reviewers (AT/SLO). The quality of the studies will be reviewed using the International Society for Pharmacoeconomics and Outcome Research (ISPOR) Consolidated Health Economic Evaluation Reporting Standards (CHEERS) (10). Data will be assessed with a process to resolve differences. Risk of bias due to missing results will be assessed. Additional information will be sought from study investigators if required information is unclear or unavailable in the study publications/reports. Certainty of findings will not be assessed.

Data

Synthesis [15]

Due to the expected heterogeneity of economic evaluations, a meta-analysis will not be conducted. Instead, a rigorous narrative synthesis will evaluate study quality, methodological differences, and robustness. Studies will be systematically described and grouped based on PICO criteria, see chapter “Eligibility criteria”. Any discrepancies in interpretation will be resolved through discussion between reviewers. Studies will also be categorized according to methodology and strategy type. Key data will be tabulated for clarity, and relationships between studies will be analyzed qualitatively, focusing on methodological variations, sensitivity analyses, and potential biases. According to the given data availability patient’s subgroups by diagnosis, age, gender and by type of treatment will be separately presented additionally.

Confidence in cumulative evidence [17]

For trial-based economic evaluations the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) – approach including risk of bias assessment will be used. Findings on incremental costs/effects, cost-effectiveness ratios and uncertainty measures will be added to the evidence profiles in the respective grade-tables. In addition, results will be plotted into a cost-effectiveness plane in case common metrics (e.g. costs and quality – adjusted life years - QALYs) for included studies are applied.

Additional information

Review Status

The review is currently planned and ongoing. Pilot work as well as formal searching as well as study identification have started but not completed. Screening search results against inclusion criteria is planned to start mid of May 2025, data extraction in the beginning of June 2025, evaluation of risk of bias, quality assessment, and data synthesis are planned to start in July 2025. Writing of the findings is planned in August 2025 and dissemination to a peer-reviewed journal in September. The systematic review is planned to be finished at the end of October 2025. The current protocol version is 1.0, dated 25 March 2025.

Dissemination Plan

The findings (and the study protocol) of this systematic review will be disseminated through submission to a peer-reviewed journal, presentations at relevant academic and professional conferences, and engagement with policymakers and healthcare providers. The goal is to facilitate informed decision-making on the cost-effectiveness of integrative oncology interventions and to support their integration into cancer care policies.

List of abbreviations

PROSPERO, International Prospective Register of Systematic Reviews; PRISMA-P, PRISMA for Systematic Review Protocol; CCCTIM, Charité Competence Center for Traditional and Integrative Medicine; FIH, Research Institute Havelhöhe; IVAA, International Federation of Anthroposophic Medical Assocations; IO, integrative oncology; TCIH, Traditional, Complementary, and Integrative Healthcare; PICO, Population, Intervention, Comparison, Outcome; CINAHL – Cumulative Index to Nursing and Allied Health Literature; ISPOR, International Society for Pharmacoeconomics and Outcome Research; CHEERS, ISPOR Consolidated Health Economic Evaluation Reporting Standards; ICER, cost-effectiveness ratio; CBR, cost-benefit ratio.

Declarations

Authors approval

All authors have seen and approved the manuscript.

Competing interests

FS reports grants from Helixor Heilmittel GmbH (travel costs and honoraria for speaking), grants from AstraZeneca (travel costs and honoraria for speaking), grants from Abnoba GmbH, and grants from Iscador AG, outside the submitted work. The other authors declared that they have no competing interests. No payment was received for any other aspects of the submitted work. There are no patents, products in the development, or marketed products to declare. There are no other relationships/conditions/circumstances that present a potential conflict of interest.

Patient and public involvement

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

Data Availability Statement

Any material required to support the protocol can be supplied on reasonable request.

Acknowledgement

We would like to acknowledge Tido von Schoen - Angerer, Adrianne Waldt, and Almut Altmann involved in the OCEANic project in supporting the present work.

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Supplementary figures and tables

Supplementary table S1. PRISMA-P 2015 Checklist

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	1
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	3
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	3
Support					
Sources	5a	Indicate sources of financial or other support for the review	☐	☒	
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	3
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	3
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	3
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	4
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	4
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	5
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	5

STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	6
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	6
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	6
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	7
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	7
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	7
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	7
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☐	☒	
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☒	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☐	☒	
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☐	☒	
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☒	☐	8

PRISMA-P 2015 Checklist, adapted for the use with protocol submissions to Systematic Reviews from Moher et al. 2015, Table 3 (12)