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Comparative effectiveness of interventions for cancer treatment–related cognitive impairment in adult cancer survivors: protocol for a systematic review

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Abstract

Background Cancer treatment–related cognitive impairment (CTRCI) can substantially reduce the quality of life of cancer survivors. Many treatments of CTRCI have been evaluated in randomized controlled trials (RCTs), including psychological interventions, pharmacologic interventions, and other therapies. There is a pressing need to establish the benefits and harms of previously studied CTRCI treatments. The proposed systematic review and network meta-analyses will assess the relative efficacy and safety of competing interventions for the management of CTRCI.

Methods In consultation with the review team, an experienced medical information specialist will draft electronic search strategies for MEDLINE®, Embase, CINAHL, PsycINFO, and the Cochrane Trials Registry. We will seek RCTs of interventions for the treatment of CTRCI in adults with any cancer, except cancers/metastases of the central nervous system. Due to the anticipated high search yields, dual independent screening of citations will be expedited by use of an artificial intelligence/machine learning tool. The co-primary outcomes of interest will be subjective and objective cognitive function. Secondary outcomes of interest will include measures of quality of life, mental and physical health symptoms, adherence to treatment, and harms (overall and treatment-related harms and harms associated with study withdrawal), where feasible, random-effects meta-analyses and network meta-analyses will be pursued. We will address the anticipated high clinical and methodological heterogeneity through meta-regressions, subgroup analyses, and/or sensitivity analyses.

Discussion The proposed systematic review will deliver a robust comparative evaluation of the efficacy and safety of existing therapies for the management of CTRCI. These findings will inform clinical decisions, identify evidence gaps, and identify promising therapies for future evaluation in RCTs.

Keywords Chemotherapy-related cognitive impairment, Systematic review, Network meta-analysis

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Introduction

While newer cancer therapeutics, such as adjuvant curative chemotherapy, have acted to substantively improve patient survival since the 1970s [1], they also come with potential survivorship issues, including cancer treatment-related cognitive impairment (CTRCI), which historically has also been called "chemo-fog" or "brain fog." Those who develop CTRCI can have notably reduced quality of life (QoL); however, effective treatment options for the condition remain elusive. As the number of cancer survivors increases globally, so does the number of people who suffer with CTRCI. There is a pressing need to better contextualize the treatments for CTRCI following cancer therapy to improve the QoL of vulnerable cancer survivors. We propose a systematic review with network meta-analyses (NMAs) to determine the scope of treatments trialled for CTRCI, as well as their relative efficacy and safety.

More broadly, the etiology of cancer-related cognitive impairment is suspected to be multi-factorial, including being related to various surgical, chemotherapeutic, radiation, and endocrine therapies [2–9]; patient-level biological, genetic, behavioral, and psychological factors [10–19]; and the presence of cancer itself [13, 20]. The consequences of cancer-related cognitive impairment can be particularly significant for older persons [21]. The direct cognitive impacts of cancers other than those of the brain and central nervous system (CNS) are unanticipated and not entirely understood and, although difficult to disentangle from the cognitive impacts of cancer therapy, are postulated to be common [11, 22, 23], afflicting from 18 to 81% of survivors of breast, prostate, and colorectal cancer [22]. Deteriorations of memory, processing speed, and executive function are most common [24] and even objective assessments of mild-to-moderate impairment can result in significant adverse impacts on daily function and QoL [25, 26], resulting in difficulties in returning to work, issues with maintaining relationships, and an overall sense of disempowerment [27–34]. Subjective complaints often do not correlate well with objective testing, with cancer survivors frequently reporting greater impacts on perceived cognition than their performance on neurocognitive testing would suggest [13]. This discordance may be due to comorbid factors, such as anxiety, depression, fatigue, recall bias, and/or insomnia negatively influencing the survivor's subjective perception of cognition more than objective measures of cognitive performance [35]; compensatory neuroplasticity of the brain that improves objective performance in a quiet and structured testing environment but not in the disorder of day-to-day life [13]; or poor sensitivity and specificity of traditional objective testing tools to detect subtle cognitive changes [13]. Although often transient [13], cognitive impairments can be persistent, lasting months to years in over 30% of survivors of cancer [32]. Additionally, attention and memory impairments may secondarily reduce cancer treatment compliance and retention in follow-up care [11]. The role of cancer treatments (i.e., systematic treatments such as chemotherapy or hormonal/endocrine therapy) is commonly believed to have a prominent impact on long-term changes in cognitive function. Therefore, effective treatment of CTRCI may improve overall cancer outcomes.

Given the substantial long-term impact that CTRCI can have on the QoL of cancer survivors, multiple treatments have been evaluated through randomized controlled trials (RCTs), including (1) psychological interventions, such as cognitive behavioral therapy (CBT), cognitive rehabilitation, and mindfulness-based stress reduction (MBSR); (2) pharmacologic interventions, such as psychostimulants and anti-depressants; and (3) other therapies, such as neurostimulation (e.g., transcranial direct current stimulation), physical exercise, yoga, music therapy, and complementary and alternative medicine (CAM) interventions [36]. Three recent systematic reviews with NMAs have been published [37–39]; however, certain limitations are apparent in the scope (e.g., focused on either non-pharmacologic or psychological interventions; restricted to breast cancer patients only; restricted to cognitive impairment outcomes, sometimes only subjective measures) and methodology (e.g., incomplete search strategies, resulting in low citation yields; minimal reporting of statistical methods, with no descriptions of how heterogeneous outcome measurement tools were addressed) of these reviews. Given these limitations and the ongoing publication of new trials, we propose a systematic review with NMAs to determine the comparative efficacy and safety of all interventions that have been evaluated in RCTs for the treatment of CTRCI.

Study objectives

We will conduct a systematic review incorporating NMAs, where feasible, to answer the following question: *What are the relative benefits and harms associated with psychological, pharmacologic, and other interventions for CTRCI in adult non-CNS cancer survivors?*

Review methods

Protocol and registration

This protocol has been drafted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Protocols (PRISMA-P) [40] and registered with the Open Science Framework (https://osf.io/qvbs8).

Review guidance

The methods for the described systematic review and NMA will follow established methodological guidance from the Cochrane Collaboration [41] and the Decision Support Unit of the National Institute for Health and Clinical Excellence (NICE), London [42–44].

Eligibility criteria

Table 1 presents the Population-Intervention-Comparator-Outcome-Study design (PICOS) criteria that will be used to determine the eligibility of studies for inclusion in the systematic review.

Data sources and search strategy

Using the Ovid platform, an experienced information specialist will draft search strategies for MEDLINE®, Embase, PsycINFO, and the Cochrane Central Register of Controlled Trials (CENTRAL). We will also search CINAHL on Ebsco (Appendix 1). A combination of controlled vocabulary ("Chemotherapy-Related Cognitive Impairment," "Neoplasms," "Cognitive Dysfunction") and keywords (e.g., chemo-fog, cancer, executive function) will be used, with no date restrictions, and a filter to limit search results to RCTs. Searches will be peer reviewed by a second information specialist using the Peer Review of Electronic Search Strategies (PRESS) Checklist [45].

A separate search will be developed to identify relevant systematic reviews, and reference lists of any relevant systematic reviews will be inspected for eligible RCTs. Grey literature searches will be guided by *Grey Matters* [46], with input from team members regarding other resources (e.g., clinicaltrials.gov), and undertaken for a total of 35 h by a review team member.

Study selection process

Search results will be amalgamated and de-duplicated using EndNote Version 9.3.3 [47] and then uploaded to the online systematic review management platform DistillerSR® (Version 2023.2.2. Evidence Partners; 2023. https://www.evidencepartners.com). Dual independent screening of titles and abstracts (Level 1) and potentially relevant full texts (Level 2) will be facilitated by screening forms in DistillerSR®. To ensure consistent application of eligibility criteria by reviewers, screening forms will initially be piloted on batches of 50–100 citations (Level 1) and 5 full texts (Level 2), with screening questions adapted in an iterative manner if needed, until reviewer agreement reaches ~ 95%. Conflicts

Table 1 Review eligibility criteria guided by the PICOS framework

PICOS domain	Inclusion criteria
Population	Adults (≥ 18 years) who were diagnosed with cancer of any type (except central nervous system (CNS)-related tumors/metastases) during adulthood and who received prior systemic treatment (i.e., chemotherapy, hormonal/endocrine therapy, or immunotherapy), alone or in combination with other treatments (e.g., concurrent radiotherapy), and who experienced cancer treatment-related cognitive impairment (CTRCI) as defined by any criteria. Studies that did not exclusively select participants based on the presence of CTRCI but that selected based on a CTRCI-associated condition (e.g., fatigue, insomnia, depression, stress, anxiety) will be included during title/abstract screening, and their full texts will be reviewed to determine if cognitive function was measured at baseline and relevant subgroup analyses were reported specific to those with CTRCI at baseline. If a subgroup analysis of participants with CTRCI at baseline was reported in the full text, the study will be retained. Studies with mixed populations of individuals with and without CTRCI at baseline will be excluded unless subgroup analyses were reported in the full text. Studies including participants actively receiving systemic therapy will be excluded because the focus of the CTRCI intervention would be on prevention not treatment. An exception to this would be people with cancer undergoing long-term hormonal therapy, such as tamoxifen or androgen deprivation therapy.
Intervention	Interventions to treat existing CTRCI (i.e., not prevent future CTRCI), including the following, alone or in combination: - *Psychological interventions*: cognitive behavioral therapy (CBT), cognitive rehabilitation or training, transcranial direct current stimulation, etc - *Pharmacologic interventions*: methylphenidate, modafinil, armodafinil, donepezil, erythropoietin, fluoxetine, memantine, ramipril, lithium, pioglitazone, etc - *Other interventions*: exercise programs, mindfulness-based stress reduction (MBSR), music therapy, Tai chi/qigong, yoga, acupuncture, light therapy, herbal supplements, nutraceuticals (e.g., omega-3 fatty acids), etc All doses, frequencies, and durations of treatment will be eligible; however, we will consider the use of different nodes in network meta-analyses (NMAs) where these vary notably between studies. We will exclude studies evaluating interventions to prevent the development of CTRCI, as well as studies that do not report sufficient intervention detail (e.g., missing descriptions of psychological interventions, missing dosages of pharmacologic interventions).
Comparator	Any of the above interventions, placebo, treatment as usual, wait list, or no treatment
Outcome	The co-primary outcomes of interest for this review will be subjective and objective cognitive function. Secondary outcomes of interest will include measures of QoL/health-related QoL (e.g., Quality of Life Index–Cancer Version (QLI-C), Quality of Life–Cancer Survivor (QOL-CS)), mental and physical health symptoms (e.g., SF-36 composite scores), adherence to treatment, and harms, including overall and treatment-related harms, and harms associated with study withdrawal. Immediate effects will not be relevant (e.g., measured the same day as interventions administered).
Study design	Both parallel group and cross-over RCTs. Abstracts, commentaries, and letters will be excluded.

identified during screening of the remaining citations will be resolved through discussion or input from a third reviewer.

In the context of high citation search yields, Level 1 screening will be aided by the artificial intelligence/machine learning (AI/ML) tool in DistillerSR® [48]. A training set of 200 citations consisting of a small number of citations that are known to be relevant, and a random sample of citations of unknown relevance will be screened by reviewers, thereby exposing the AI/ML tool to both relevant and non-relevant citations. After this training exercise, the remaining citations in the database will receive relevance scores generated by the AI/ML tool (i.e., estimates of the probability of meeting Level 1 eligibility criteria). The citations will then be ordered from high to low relevance score for screening by reviewers, and as they are screened, the AI/ML tool will continue to learn, adjusting relevance scores and reordering citations throughout Level 1 screening. Conflicts occurring during Level 1 screening will be resolved frequently to optimize the accuracy of the screening decisions upon which the AI/ML tool learns. Over time, the number of newly identified citations meeting Level 1 eligibility criteria will decline, and the proportion of the predicted relevant references found (a measure estimated by the AI/ML tool) will increase. When this proportion reaches 95%, the yield of new relevant citations will be minimal, and the AI/ML tool will be applied to act as a single reviewer to exclude the remaining references. These references will be screened by a single human reviewer, with screening discrepancies resolved by a second reviewer. Thus, the risk of omissions resulting from use of the AI/ML tool will be minimized, and the efficiency Level 1 screening will be optimized.

Data extraction

Data extraction with verification by a second reviewer will be guided by standardized forms in DistillerSR®, following a pilot exercise of batches of three included studies. Conflicts will be resolved through discussion or mediation of a third reviewer until consensus is reached. The following data will be extracted from publications:

- Publication information: first author's last name, year of publication, funding source, country of conduct
- Interventions compared: psychological, pharmacologic, other, placebo/usual care/no treatment/wait list; measures of treatment intensity (e.g., dose, frequency, duration); mode of delivery [49] (e.g., in-person/virtual for psychological interventions); intervention setting [49] (e.g., individual or group for psychological interventions)
- Study enrolment criteria: cancer type, CTRCI diagnostic criteria used, and any patient assessments of functional or neurologic status
- Demographics of study sample: sex/gender; race/ethnicity; mean/median age or age subgroups; socioeconomic status/education; cancer type and stage; relevant genetic traits [13, 50, 51] and biotypes [12, 15]; study baseline (i.e., pre-intervention) measures of cognitive function [24] and symptoms of or diagnoses of mental health disorders (e.g., depression, anxiety, fatigue, and dementia); type(s) of cancer treatment received [24] (e.g., chemotherapy, radiation therapy) and whether curative or palliative/metastatic; use of selective serotonin reuptake inhibitors (SSRIs) [24] or other anti-depressants; baseline measures of inflammation [13] (e.g., tissue necrosis factors, interleukins, etc.)
- Outcome data: outcome definitions (e.g., tools and cut-offs used), measurement timing, data format (e.g., dichotomous presence/absence or continuous measures), and associated values of quantitative data for the following outcomes:
    - Co-primary outcomes: changes in subjective and objective cognitive function
    - Secondary outcomes: changes in symptoms of depression, anxiety and stress; QoL, activities of daily life (ADLs), harms (overall and treatment-related), and dichotomous measures of withdrawals due to adverse events (AEs) or any cause as measures of tolerability

All of the above outcomes will be extracted, and each study's primary outcome(s) will be flagged.

- Summary of RCT authors' conclusions

Primary outcomes

In consultation with our clinical experts and the background literature, we selected cognitive function, measured both subjectively and objectively, to be co-primary outcomes for this review. Subjective perceptions of cognitive function often do not correlate well with objective measures [13, 52]; thus, we will perform separate syntheses for both, as has been done in previous systematic reviews [37–39]. The International Cognition and Cancer Task Force (ICCTF) advises that three domains of cognitive function are most impaired by chemotherapy—learning and memory, processing speed, and executive function [24]—and recommends three assessment tools to objectively measure them: Hopkins Verbal Learning Test-Revised (HVLT-R), measuring verbal memory and delayed recall; the Trail Making Test (TMT), measuring

psychomotor speed and executive function; and the Controlled Oral Word Association test (COWAT) of the Multilingual Aphasia Examination, measuring speeded lexical fluency and executive function [13, 24, 32]. These tests were selected by the ICCTF because they combine adequate sensitivity to measure their respective cognitive domain(s) and adequate psychometric properties (e.g., test-retest reliability), with suitability for multinational application and alternative forms [24]. Similar cognitive assessment measures have also been suggested [32] that do not meet all ICCTF criteria. Additional assessments of working memory (i.e., executive function and complex attention) were also encouraged by the ICCTF; however, no tests met their recommendation criteria [24]. Similar to a recent Cochrane review [53], if sufficient data are available, we may consider the three cognitive domains recommended by the ICCTF (or their subdomains) as separate co-primary objective cognitive function outcomes and other domains as secondary outcomes (e.g., complex attention, language/verbal skills, sensation/perception/motor skills [54]). However, other recent systematic reviews have identified high diversity in the tests used to measure cognitive function in people who have undergone cancer therapy—over 38 different self-reported measures [52] and over 70 different objective psychological tools [55–57]—many of which measure more than one cognitive function domain (Table 2). We anticipate that the use of tools and batteries of tests that are non-specific to a discrete cognitive function domain or subdomain may preclude a domain-based analytic approach [24]. The final decision regarding the analytic approach will be made in consultation with our clinical experts, once the scope of the measurement tools used in the included studies has been established.

Risk of bias assessment

We will use the Cochrane Risk of Bias (ROB) Tool for RCTs [58] for assessment of ROB at the outcome level. All seven domains of the Cochrane ROB tool will be considered, with the last domain, "Other bias," to include (1) significant imbalances in baseline key demographic variables between groups, (2) use of outcome assessment measures with low reliability or validity, and (3) industry funding sources and potential conflicts of interests of the researchers. Imbalances between groups of demographic variables at baseline may indicate insufficient randomization of subjects and unmeasured confounding, warranting an unclear assessment of ROB. When imbalances occur in key demographic variables and they are not controlled through analytic means, a high ROB will be assigned. Key demographic variables will vary by outcome; for our co-primary outcomes, baseline subjective and objective measures of cognitive impairment [53], proportions of participants with other confounding conditions (e.g., sleep disorders, depression, anxiety, endocrine dysfunction), and proportions of participants using SSRIs [24] will be considered key demographic variables. Regarding outcome assessment measures, cognitive

Table 2 Psychological tools commonly used in the literature to measure objective and subjective cognitive function (taken from Bray et al. [52], and Saita et al. [56])

Subjective cognitive function tools [52]	Objective cognitive function tools [56]
• European Organisation for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30)–Cognitive Functioning (EORTC-CF) • Functional Assessment of Cancer Therapy-Cognitive Function (FACT-COG) • Cognitive Failures Questionnaire (CFQ) • Multiple Ability Self-report Questionnaire (MASQ) • Patient's Assessment of Own Functioning Inventory (PAOFI)	• Block design • Boston naming test • California Verbal Learning Test (CVLT) • Cambridge Neuropsychological Test Automated Battery (CANTAB) • Controlled Oral Word Association Test (COWAT) • Digit span test • Digit symbol/digit symbol substitution (coding) test • Hopkins Verbal Learning Test (HVLT) • Letter number sequencing • Logical memory • Mini-Mental State Examination (MMSE) • Montreal Cognitive Assessment (MoCA) • National Adult Reading Test (NART) • Paced Auditory Serial Addition Test (PASAT) • Rey Auditory Verbal Learning Test (RAVLT) • Rey-Osterrieth Complex Figure test (ROCF) • Sorting test • Stroop test • Trail making test (TMT) • Verbal Fluency Test (VFT) • Vocabulary • Wechsler Adult Intelligence Scale (WAIS) • Word reading

function assessment tools for populations without cancer may be unreliable or invalid when used among people living with cancer [53]. Assessment tools recommended by the ICCTF have adequate reliability and validity in cancer research and will be considered to have low ROB [24]. For other tools, the reliability and validity of the tool specific to people with cancer must be reported by study authors to be assessed a low ROB. Two reviewers will independently assess each study, with conflicts resolved through discussion or arbitration by a third reviewer. The overall ROB for a given outcome will be the highest level assigned to any domain for that outcome (i.e., all domains must have been assessed to be of low ROB for a low overall ROB to be assigned). Results of ROB appraisals will be summarized across studies, using the primary outcome of each study, and visualized with summary plots generated using the online *robvis* application (https://mcguinlu.shinyapps.io/robvis/) [59].

Within each outcome, for all pairwise comparisons for which 10 or more studies have been included in the NMA, we will assess publication bias and small-study effects. Funnel plots will be generated as graphical displays of the assessments [60].

Synthesis and analysis

The data extracted into DistillerSR® will be downloaded into Excel [61] spreadsheets for data cleaning and development of initial study characteristic summaries. A map of the assessment tools used to measure objective cognitive function will also be developed at this time to guide selection of the most appropriate analytic approach for that outcome (e.g., a single analysis for overall objective cognitive function, three separate analyses for the domains of cognitive function suggested by the ICCTF, or analyses by subdomain).

Feasibility assessment for NMA

For all outcomes, we will determine the feasibility of conducting NMAs based on two concepts: the clinical and methodological heterogeneity across the available studies and the connectivity of the network [62]. Explorations of between-trial heterogeneity will examine the similarity of study populations (i.e., inclusion/exclusion criteria, baseline participant characteristics), interventions, and baseline control group risks or scores. We describe anticipated sources of heterogeneity relevant to the assumption of transitivity within the "Proposed additional analyses" section below, and we will examine for between-study differences in such characteristics using bar plots, box plots, inspection of evidence tables, and other strategies. Potential outlier studies that may contribute substantially to heterogeneity will also be identified, as will studies assigned a high overall ROB for the outcome. Explorations of between-trial heterogeneity will also help the review team determine if there are common treatment comparators that can act as anchors, as well as common outcome definitions across studies. Elements of trial design will also be considered, including heterogeneity of follow-up duration. For each outcome, we will generate a network diagram. All intervention types will be allowed into each network (i.e., psychological, pharmacologic, and other treatments). The treatment nodes of each network will be developed through discussion with our clinical and methodological experts, with consideration of intervention type (e.g., could music therapy and MBSR be combined into a single "relaxation therapy" node?), dose, frequency, and duration. We will also explore grouping of psychological interventions according to proposed evidence-based classification systems for psychological interventions [63, 64], as was considered in a recent Cochrane review [53]. Thought will be given by the study team to determine if various control group interventions (e.g., placebo, treatment as usual, waitlist, other supportive therapy) should be considered one or multiple treatment nodes in the network. Other treatment nodes will be either "lumped" or "split" based upon the above consultations and explorations to generate a network that is both clinically relevant (e.g., group or individual nature of psychological and activity-based interventions, doses of pharmacological interventions, durations of therapy) and structurally robust. When a network is deemed to be too sparse to produce valid comparative estimates for an outcome (e.g., the number of interventions is larger than the number of included studies) or there is strong evidence that the transitivity assumption is not appropriate, an NMA will not be conducted, and either pairwise meta-analyses or descriptive summaries will be used to synthesize the available evidence.

Approach to direct intervention comparisons

For each outcome, where two or more studies report the same comparison, direct treatment effects will be explored though standard pairwise meta-analyses. All pairwise meta-analyses will be conducted in R [65] using random-effects models, with the between-study variance (τ^2) estimated using restricted maximum likelihood estimation (REML) methods and the Q-profile approach [66]. Heterogeneity will be estimated as the proportion of the observed variability in the effect estimates that is explained by variability in the underlying true effects of the included studies (I^2) [41, 67]. When I^2 is greater than zero and at least three studies are in the meta-analysis, the Knapp-Hartung-Sidik-Jonkman method will be used to estimate 95% CIs of the summary effect estimate [68]. Heterogeneity will be considered substantial when I^2 is > 50% and the p value of the Q-statistic is < 0.10 [41].

We will express study-level effect estimates as mean differences (MDs) between groups, with corresponding 95% confidence intervals (CIs) for continuous outcomes and as odds ratios (ORs), with corresponding 95% CIs for dichotomous outcomes. For continuous outcomes, we anticipate variability in the data formats reported, including mean raw pre- and post-intervention values per arm, with corresponding standard deviations (SDs); MDs per arm (i.e., the difference between pre- and post-intervention measures), with corresponding standard errors (SEs); and between-group difference of MDs, with corresponding CIs. When SDs are missing from follow-up means, they will be assumed to be equal to SDs of the baseline mean values. When only raw data are reported, we will calculate the MD and SE in each arm, if it is appropriate to assume a correlation between mean pre- and post-intervention values. We anticipate different measurement tools/scales to have been used across and within studies [52, 55, 56] (e.g., processing speed measured with different subsets of the Wechsler Adult Intelligence Scale (WAIS) or the Delis-Kaplan Executive Function System (D-KEFS)). We will explore statistical combinability by estimating continuous effect sizes as standardized mean differences (SMDs) to maximize data usage. We will adopt a data-driven approach to dealing with other aspects of effect size multiplicity, guided by recent literature [69].

Approach to NMA

Where feasible, random effects frequentist NMAs will be conducted to compare the relative efficacy of the competing interventions, using the *netmeta* package in R [42–44]. For random effects models, a common between-trial variance will be assumed [42]. Where timing of outcome measures differs across studies, we will determine the most appropriate strategy to manage this heterogeneity within NMAs through examination of patterns of reported follow-up times and consultation with our clinical experts. The consistency assumption will be tested locally using the loop-specific method [70] and globally using the design-by-treatment interaction test [71]. A common heterogeneity parameter will be assumed across all treatment comparisons, and the between-study variance (τ^2) will be estimated for each outcome. The heterogeneity parameter will be compared to the appropriate empirical distribution [72, 73], and statistical heterogeneity will be assessed to be low, moderate, or high based upon the first and third quantiles of the distribution.

Summaries of findings from the final NMA model for each outcome will include reporting of a league table of the relative treatment effects and their uncertainty (i.e., 95% CIs), measures of treatment hierarchy [74], and a rank-heat plot to present all outcome results in a single plot (https://rankheatplot.com/rankheatplot/) [75]. All NMAs will be conducted in R [65]. The certainty of the evidence for the co-primary outcomes will be assessed as high, moderate, low, or very low, using the Confidence in Network Meta-Analysis (CINeMA) framework [76].

For outcomes and comparisons where NMA is not feasible (e.g., poorly connected or sparse networks, disconnected comparisons), we will report findings from pairwise meta-analyses or descriptive summaries, where data from only single studies are available for a given pairwise comparison.

Proposed additional analyses

We anticipate clinical and methodological heterogeneity that may challenge the assumption of transitivity and require additional analyses to address (see "Feasibility assessment for NMA"). We will assess the transitivity assumption by visually inspecting the distributions of potential effect modifiers in the included studies across all pairwise comparisons [77] (e.g., cancer type, age, sex, genotypes, baseline cognitive status, and comorbidities of relevance) and by statistically evaluating for inconsistency [70] using the loop-specific approach [78] and the design-by-treatment interaction approach [71]. To address heterogeneity, we intend to conduct meta-regressions, subgroup analyses, and/or sensitivity analyses, when sufficient data are available, as will be determined by our feasibility assessment. We anticipate potential heterogeneity across studies in follow-up times, study context (e.g., long-term care), participant eligibility criteria (e.g., cancer type/stage [79]; age [80]; definition of CTRCI [23, 79]; presence/absence of potentially confounding conditions, such as diabetes or cardiovascular disease [80]; type of prior systemic cancer therapy [24]; use of SSRIs [24]), baseline patient characteristics (e.g., age [80], proportion female [81], race [80], cancer stage [79], comorbid conditions [80], baseline cognitive function/reserve [80], education level [13, 80], genotypes [13, 50, 51] and biotypes [12, 15], mood/sleep disorders [81, 82], proportion using SSRIs [24]), intervention characteristics (e.g., dose, schedules), outcome definitions (e.g., tool and cut-off used, domains/subdomains within the outcome), and the baseline risk of the control group, all of which may modify treatment effects. If sufficient data are available, we will consider separate meta-regressions for each covariate that demonstrates substantial heterogeneity that may act as a treatment effect modifier. Where data are insufficient, subgroup analyses will be explored to investigate the impact of the covariates of interest on treatment effects. In the presence of insufficient data for subgroup analyses, outlier studies will be removed from the network and sensitivity analyses conducted to evaluate the robustness of the findings. A similar approach

will be used to investigate the impact of studies with high overall ROB on NMA findings.

Descriptive syntheses

Where a paucity of data precludes quantitative analysis, either NMA or pairwise meta-analysis, we will descriptively summarize the findings from individual studies, with supporting tables and figures.

Patient and public involvement

In planning this research, input was sought from multiple organizations representing people with lived experience during the preparation phase regarding elements of its design to ensure that our findings would be relevant to patients and other stakeholders. We wish to thank Ontario Health, the CURE Foundation and the Canadian Association of Nursing Oncology/Association Canadienne des Infirmières en Oncologie for their contributions to this initiative.

Reporting

Reporting of the final systematic review will be guided by the PRISMA extension statement for NMAs [83]. The availability of literature and its progress through the review process will be depicted with an evidence flow diagram [84]. All raw data, including ROB assessments, will be publicly available on the publishing journal's website, alongside the open-access manuscript.

Discussion

Cancer treatment–related cognitive impairment remains incompletely understood, with ongoing research into the domains of cognitive function that are affected, as well as its incidence, risk factors, mechanisms, and treatment. Several systematic reviews with meta-analyses [49, 53, 85–92] and NMAs [37–39] have been published. However, to our knowledge, none of the existing reviews have encompassed all of the following: a comprehensive literature search; inclusion of all relevant cancer types; analyses of subjective and objective measures of cognitive impairment, plus secondary outcomes; rigorous methods to address heterogeneity of outcome assessment tools; and comparisons of the relative effects of all intervention types, including psychological, pharmacologic, and other treatments in network meta-analyses. We will employ sound methodology in the planned systematic review, harnessing both direct and indirect evidence in rigorous analyses to provide new informative evidence regarding the comparative efficacy of competing interventions for CTRCI.

Based on previous systematic reviews, we anticipate several challenges and potential limitations with the available evidence. Recent NMAs of non-pharmacologic interventions have identified sufficient studies to review (e.g., almost 30 studies [37, 39]), and given our broader eligibility criteria, we expect to find a sufficient volume of evidence. However, substantial clinical and methodological heterogeneity across studies will need to be addressed with rigorous methods (e.g., use of SMDs, development of composite outcome measures for batteries of tests, evidence-based categorization of interventions), or NMA may be precluded. One previous systematic review reporting NMAs attempted to decrease clinical and methodological heterogeneity by restricting the review eligibility criteria, similar to the criteria that we propose [37]. Despite this approach, statistical heterogeneity was found to be high for the memory outcome, which was interpreted to be due to "memory" being a composite outcome of its various subdomains that may have had different intervention effects. Other systematic reviews with NMAs have ignored clinical and methodological heterogeneity and the assumption of transitivity entirely [38, 39]. To address heterogeneity of intervention effects within an outcome, we will explore the feasibility of using smaller-scale outcomes (e.g., using the subdomains of the memory domain); however, the use of outcome measures that do not map to a discrete subdomain may preclude this approach. Systematic reviews attempting pairwise meta-analyses have also been limited by the available evidence. A review of pharmacologic agents for cancer-related cognitive impairment in 2019 focusing on cognitive function could not conduct meta-analyses because of lack of availability of some key quantitative outcome data, methodological heterogeneity, and lack of generalizability to cancer survivors with cognitive impairment [88]. Half of the included studies focused on fatigue as their primary outcome not cognitive function; thus, intervention doses and outcome assessment tools were not optimized to evaluate cognitive function, and the power to detect a difference in cognitive function was low [88]. As well, all but one of the included studies did not test for cancer-related cognitive impairment in participants prior to randomization, calling into question the generalizability of study findings to cancer survivors with cognitive impairment, the review's target population [88]. The eligibility criteria of our review will restrict inclusion to trials that only include cancer survivors with CTRCI; while this may reduce the number of included studies, it will ensure the external validity of findings. Finally, we anticipate several sources of bias in the available literature that may limit the interpretation of our review findings. While numerous studies may meet our review eligibility criteria, small-study effects may bias some NMA effect estimates, as was found in a recent systematic review of the effects of non-pharmacological CTRCI interventions in breast cancer survivors [49]. As well, the risk of bias and

the methodological quality of the included studies may negatively impact the robustness of the review's conclusions [53]. If possible, we will conduct sensitivity analyses to determine the impact of studies with high risk of bias or low methodological quality on effect estimates.

This will be the first comprehensive systematic review with NMA of all interventions to treat CTRCI in survivors of all cancer types, except CNS tumors/metastases, that will use rigorous methodology to synthesize the available evidence. We will publish the findings of this review in an open-access peer-reviewed journal to enhance knowledge transfer to researchers and clinical oncologists. In keeping with an integrated knowledge translation approach, the concept and design of this review were developed collaboratively with knowledge users from societies and groups with patient-centered mandates. Lay summaries and knowledge mobilization products will be developed for patients, decision-makers, clinicians, and nurses and will be disseminated through our knowledge user websites, social media, and other forums. The findings from this review will be instrumental in guiding the design of much needed high-quality prospective studies of interventions to treat CTRCI in cancer survivors.

Abbreviations

ADL	Activities of daily life
AE	Adverse event
AI/ML	Artificial intelligence/machine learning
CAM	Complementary and alternative medicine
CBT	Cognitive behavioral therapy
CNS	Central nervous system
CTRCI	Cancer treatment–related cognitive impairment
MD	Mean difference
NMA	Network meta-analysis
OR	Odds ratio
PICOS	Population–Intervention–Comparators–Outcomes–Study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL	Quality of life
RCT	Randomized controlled trial
ROB	Risk of bias
SMD	Standardized mean difference

Supplementary Information

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Supplementary Material 1. Appendix 1. Literature Search Strategies.

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Disclaimer

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Authors' contributions

Study conception: BH, MC. Acquisition of funding: BH, CH, DR, SK, KR, SM, MC. Methods development: DW, BH, AAV, SK, KR, MC. Preparation of initial protocol draft and subsequent revisions: DW, BH. All authors (DW, CH, DR, AAV, BS, SK, KR, SM, LF, ML, DS, LV, IM, MC) read and approved the final protocol. BH is guarantor of the protocol.

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Availability of data and materials

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Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

BH has previously received honoraria from Eversana Inc for the provision of methodologic advice related to systematic reviews and meta-analysis. All other authors report no conflicts of interest to declare.

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