AK-Neuro: A tailored exercise oncology program for neuro-oncology patients – Study protocol

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ABSTRACT

Background: Patients with primary brain tumours (i.e., neuro-oncology patients) lack access to exercise oncology and wellness resources. The purpose of the Alberta Cancer Exercise – Neuro-Oncology (ACE-Neuro) study is to assess the feasibility of a tailored neuro-oncology exercise program for patients across Alberta, Canada. The primary outcome is to assess the feasibility of ACE-Neuro. The secondary outcome is to examine preliminary effectiveness of ACE-Neuro on patient-reported outcomes and functional fitness.

Methods: Neuro-oncology patients with a malignant or benign primary brain tumour that are pre, on, or completed treatment, are >18 years, and able to consent in English are eligible to participate in the study. Following referral from the clinical team to cancer rehabilitation and the study team, participants are triaged to determine their appropriateness for ACE-Neuro and other cancer rehabilitation services (including physiatry, physiotherapy, occupational therapy, and exercise physiology). In ACE-Neuro, participants complete a tailored 12-week exercise program with pre-post assessments of patient-reported outcomes and functional fitness, and objective physical activity tracked across the 12-week program. ACE-Neuro includes individual and group-based exercise sessions, as well as health coaching.

Conclusion: We are supporting ACE-Neuro implementation into clinical cancer care, with assessment of needs enabling a tailored exercise prescription.

Abbreviations: TBCC, Tom Baker Cancer Centre; CCI, Cross Cancer Institute; REDCap, Research Electronic Data Capture; PAR-Q+, Physical Activity Readiness Questionnaire; PROs, Patient-Reported Outcomes; KPS, Karnofsky Performance Status; ECOG, Eastern Cooperative Oncology Group; FITT, Frequency, Intensity, Time, Type; SPPB, Short Physical Performance Battery; RPE, Rating of Perceived Exertion; ESAS-r, Revised Edmonton Symptom Assessment System; GLTEQ, Godin Leisure-Time Exercise Questionnaire; FACT-B, Functional Assessment of Cancer Therapy-Brain; FACT-Cog, Functional Assessment of Cancer Therapy-Cognition; FACIT-F, Functional Assessment of Chronic Illness Fatigue Scale; CSEP, Canadian Society for Exercise Physiology; WAT, Wrist-worn Activity Tracker; MCID, Minimum Clinically Important Difference; RE-AIM, Reach, Effectiveness, Adoption, Implementation, Maintenance.

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1. Background

While there is evidence supporting the role of exercise and physical activity for all individuals living with cancer [1], certain tumour groups, including patients with primary brain tumours (i.e., neuro-oncology patients), are underrepresented in this literature [2]. Primary brain tumours are defined as tumours that start in the brain cells. They rarely spread outside of the central nervous system [3]. Patients with primary brain tumours are often presented with poor survival prognoses and undergo intensive treatments that result in cognitive and physical impairments, impacting activities of daily living (e.g., speech, balance, coordination), as well as quality of life [2, 4–6]. In Canada, Glioblastoma is the most commonly diagnosed brain cancer in adults [7]. As a cancer population with a median survival of 12–14 months, and 5-year survival rate of 1% for adults over 55 [8], supporting patients to engage in exercise and physical activity may aid in supporting wellness and enhancing quality of life. Other primary brain tumours, even if they grow slowly (i.e., low-grade meningiomas), can significantly affect the quality of life of patients, including the younger adult population. To improve effectiveness, a multidisciplinary collaboration across the medical, rehabilitation, and exercise specialist teams to enhance access to tailored exercise resources is essential [2, 9, 10].

Exercise work to date in neuro-oncology has been limited, with the few studies supporting exercise feasibility and potential impacts, including decreasing symptom burden and improving physical function, cardiorespiratory fitness, cognition, quality of life, and emotional well-being [11–13]. Given the early state of this literature, work must continue to assess the role of exercise for individuals with brain tumours, and in particular assess the feasibility of implementation into clinical care and how to best tailor exercise based on the unique needs and significant treatment-related side effects that remain a major burden and negatively impact quality of life in this patient population [14–17].

Within Alberta, Canada, we have implemented the Alberta Cancer Exercise (ACE) program [18] over the past five years, and effectiveness is currently being assessed in a dataset of over 2300 participants. However, ACE primarily includes participants from breast, prostate, and colorectal tumour groups. Thus, there remains a critical need for clinical workflows to support building exercise referral into the cancer care system specifically for underserved populations, such as neuro-oncology. Building from ACE, and with a focus on co-creation of tailored programming with patients, clinicians, and researchers, our work aims to [1]: provide a tailored exercise program for neuro-oncology patients, considering addressing needs earlier in the care pathway, from diagnosis through treatment and into longer term survivorship [2]; provide models of delivery of exercise oncology programs to enhance access (i.e., remote delivery, home support, individual vs group); and [3] build this improved access systematically within the neuro-oncology clinics in Calgary and Edmonton, to ensure that all patients diagnosed with brain tumours can access supportive care resources during their cancer care journey. Given the stage of research for exercise oncology in Alberta, an effectiveness-implementation trial [19] in neuro-oncology supports development of a safe and effective program, with changes implemented based on quality improvement feedback from patient and clinical teams as needed throughout the study.

The primary outcome of this work is thus to assess the feasibility of a tailored neuro-oncology exercise program for patients (i.e., ACE-Neuro-Oncology; ACE-Neuro), being treated at the two tertiary cancer centres in Alberta—the Tom Baker Cancer Centre (TBCC) in Calgary, and the Cross Cancer Institute (CCI) in Edmonton. Feasibility includes rates of referral and enrolment, program adherence, measurement completion, and adverse event reporting. Specific outcomes related to the rehabilitation triage clinic will be reported separately. Secondary outcomes are to examine the preliminary effectiveness of the neuro-oncology exercise program on patient-reported outcomes, functional fitness, and physical activity levels. We hypothesize that ACE-Neuro will be feasible, with ≥50% eligible patients referred to ACE-Neuro, ≥50% of those enrolled will complete the intervention, ≥60% of those who complete the intervention will complete pre- and post-intervention measures, ≥40% of those who complete the intervention will complete follow-up measures, and no major adverse events will occur. We also hypothesize that ACE-Neuro will be effective, as measured by improvements in patients' physical and psychosocial well-being as well as physical activity levels (individual level outcomes), and a more integrated workflow in the clinical cancer care setting that includes exercise as part of standard clinical practice (systems level outcome).

2. Methods

2.1. Study design and procedure

This study was approved by the University of Calgary Health Research Ethics Board of Alberta (HREBA) – Cancer Committee (CC) - HREBA. CC-20-0322. Using the successful implementation model of the exercise oncology program developed in ACE, the proposed feasibility study includes a neuro-oncology cohort within a mixed methods study design.

2.2. Participants

All neuro-oncology patients with a malignant or benign primary brain tumour that are pre, on, or completed treatment in Alberta, Canada, are >18 years, and able to consent in English are eligible to participate in the study. Recruitment began in April 2021 and is expected to close in Spring 2023, with follow-up assessments concluding a year later (Spring 2024). Because the main outcome of this study is feasibility, an a priori sample size has not been calculated. Based on current clinical numbers, and previous work done with neuro-oncology patients at CCI, we anticipate approximately 25–30 eligible patients per year, per site.

2.3. Recruitment & referral

The study flow is depicted in Fig. 1. Our aim is to support referral of all eligible neuro-oncology patients to ACE-Neuro. Recruitment procedures are dependent on the site. Within Calgary (i.e., TBCC), the clinical team (consisting of oncologists and nurse practitioners) will send a referral to Rehabilitation Oncology via Cancer Care Alberta’s Putting Patients First Questionnaire in the electronic oncology booking and medical information system. The clinical team, based on their judgment, may not refer patients they deem to be ineligible, for reasons such as disease status, not being interested, unable to participate in exercise, not able to consent in English, or other clinical reasons. In Edmonton (i.e., CCI), neuro-oncology patients will be introduced to ACE-Neuro during their usual triage assessment that is conducted by an occupational therapist. Patients will be provided with a study brochure and instructed to contact the study team.

Once referred to ACE-Neuro, the study coordinator at each site contacts potentially eligible patients and presents a full introduction to the study. Patients that agree to participate are sent the study consent form via REDCap, a secure web application (Research Electronic Data Capture; REDCap) [20]. After consenting to the study, all patients undergo a two-part screening procedure prior to beginning the exercise program. In Calgary, this procedure includes the following:

1) CALGARY PART ONE SCREENING: Patients will complete health and medical history screening, including a Health History Questionnaire, an Identifying Information Questionnaire (i.e., demographics), and the Physical Activity Readiness Questionnaire; PAR-Q+. In addition, patients complete baseline patient-reported outcomes (PROs), which are further outlined below.

This screening and all questionnaires are completed via REDCap.
(2) CALGARY PART TWO SCREENING: Cancer Physiatry (i.e., physical medicine and rehabilitation) is part of the Rehabilitation Oncology clinic team at the TBCC, thus patients will attend a Neuro Oncology Rehabilitation Triage Clinic, led by a Resident Physician (LCC) and the ACE-Neuro Study Coordinator (JTD), to assess the patients’ readiness for participating in ACE-Neuro. During this 45-minute appointment, patient medical and functional history is reviewed, a full neurological examination is performed, and the Short Physical Performance Battery Protocol (SPPB) screening test is performed [21]. Based on test results, Karnofsky Performance Status (KPS) and Eastern Cooperative Oncology Group (ECOG) scores are determined and patients are subsequently triaged to ACE-Neuro, Rehabilitation Oncology (including physiatry, physiotherapy, and occupational therapy), or a combination of these services. If not initially triaged to ACE-Neuro, patients will be re-referred to the ACE-Neuro study team once deemed appropriate by their clinical team. During the COVID-19 pandemic, additional Alberta Health Services-regulated COVID-19 screening procedures will take place in advance of this in-person appointment.

In Edmonton, Cancer Physiatry is not internally offered as a Rehabilitation Oncology service within the cancer care system. Thus, as part of usual care, patients will be assessed by an occupational therapist, including completing the Short Physical Performance Battery screening test. Following self-referral to ACE-Neuro and participant consent to the study, the subsequent screening procedure includes:

(1) EDMONTON PART ONE SCREENING: A Clinical Exercise Physiologist will complete health and medical screening for participants using the Health History Questionnaire, Identifying Information Questionnaire, and the Physical Activity Readiness Questionnaire; PAR-Q+.

(2) EDMONTON PART TWO SCREENING: The Clinical Exercise Physiologist will obtain physician approval for participation in ACE-Neuro.

2.4. The exercise intervention

2.4.1. Exercise sessions

Upon entering the study, participants will be provided with a welcome package including an overview of the 12-week program, the role of exercise for neuro-oncology, understanding the FITT (Frequency, Intensity, Time, and Type) principle, instructions for using the activity tracker, educational topics and their respective handouts, and additional resources, including a Cancer and Exercise Wellness Manual. The 12-week exercise intervention will be tailored to each participant, with programs designed by an exercise specialist (Fig. 2). Following published guidelines [1], and the established ACE [18], program protocol, the program will include twice-weekly supervised exercise sessions led
by the study exercise specialist. Depending on COVID-19 restrictions and participant preferences, the intervention is delivered remotely (i.e., via Zoom), or in-person (i.e., at the University of Calgary or University of Alberta cancer and exercise-specific facilities). Session intensity will be based on participants’ acute perceptions of energy and fatigue and monitored using Borg’s Rating of Perceived Exertion (RPE; 1–10) scale [22]. Sessions will be 30–60 min, tailored to meet the unique needs of each individual and progressed over time, and overall may include the following: 5-10-min warm-up focusing on mobility and light aerobic movements (RPE ~1–3); a 15-40-min aerobic, resistance, and balance training circuit (RPE ~2–6); followed by a 10-15-min cool down, including flexibility training (RPE ~1–2). All participants start in a one-on-one format, and after two weeks of individual sessions, participants are offered a once-weekly group in-person or virtual (depending on COVID-19 restrictions) session with other ACE-Neuro participants. If participating remotely, both one-on-one and group-based sessions will be delivered via Zoom. The group session will replace one of their weekly individual sessions, and is designed to foster social connections that are central to the ACE model [18]. Finally, the exercise program will follow an “exercise and educate” framework that is based on motivational interviewing, health coaching, and health behaviour change [23,24] that includes the education topics of (1) goal setting, (2) behaviour change, (3) stress management, (4) self-compassion, (5) sleep, and (6) social support. Education topics will be discussed every two weeks at the end of the exercise session, during cool-down. In addition, participants will have the option to attend a live webinar on each topic during their 12-week program.

2.4.2. Health coaching

All participants will have the choice to participate in health coaching calls [23], provided by a health coach with exercise oncology specific training. Health coaching calls will take place weekly for 15–30 min following an individualized exercise training session, and will be delivered remotely (e.g., via end-to-end encrypted Zoom or phone call) at the participants’ preferred date and time. Health coaching calls will use a participant-centered approach, with consideration given to participant-determined discussion, self-discovery, and the coach-participant relationship [23]. Health coaching will be delivered one-on-one for the first month of the program (week 1–4), followed by group health coaching for the remainder of the 12 weeks (week 5–12), for the participants that attend the group-based classes.

To ensure consistency in both the health coaching and exercise program delivery across participants, and to ensure that the principles of health coaching are being followed during calls, fidelity checks will take place throughout the study. Ten percent of all calls and exercise sessions will be randomly selected for evaluation, and a standardized fidelity ‘checklist’ form will be completed by blind trained assessors (i.e., experts in the field; trained graduate students).

2.5. Timeline of assessments

In addition to attending the triage clinic, consenting patients will complete assessments at five timepoints (1): baseline PROs and health screening, pre-triage clinic, (2) baseline functional fitness, post triage clinic, (3) post-program (twelve weeks), (5) six months, (6) twelve months (Fig. 1). The twelve week, six month, and twelve month timepoints will all include the completion of PROs via REDCap and the assessment of functional fitness (online via Zoom or in-person). Objective physical activity will only be collected during the intervention (baseline to twelve weeks). Participants recruited in Edmonton will complete assessments at four timepoints, as they do not attend the triage clinic (i.e., baseline PROs and functional fitness occur at the same time for participants in Edmonton; Fig. 1).

2.6. Study measures

2.6.1. Demographics and clinical characteristics

Demographics and clinical characteristics will be collected via
REDCap and confirmed with chart review by the Study Coordinator (JTD) and second author (LCC) in ARIA (i.e., the electronic oncology information system). Data collected will include diagnosis and treatment details, sex, self-selected ethnicity and gender, employment status, annual family income, smoking status, alcohol consumption, and physical activity history.

2.6.2. Primary outcome: feasibility

To assess feasibility, we will track referral rate, enrolment rate, program adherence, measurement completion rate, and adverse events. All feasibility aspects of the triage clinic will be reported separately. All feasibility thresholds are based on feedback from the clinical team and other feasibility work in exercise oncology [25–28]. With the advanced nature of disease in neuro-oncology, patients often experience high symptom burden and intensive treatments. Based on discussions with the neuro-oncology clinical team, lower feasibility thresholds (i.e., 50%) were expected for recruitment and adherence results in comparison to other tumour groups.

2.6.2.1. Referral to ACE-Neuro. To examine the feasibility of referral, the number of patients referred from the clinical team to ACE-Neuro will be tracked. The pre-determined threshold is ≥ 50%.

2.6.2.2. Enrollment into the study. To examine the feasibility of enrollment, the number of patients that enrol into the study after hearing the full study introduction will be tracked. The pre-determined threshold is ≥ 50%.

2.6.2.3. Program adherence. The number of participants that complete the exercise intervention will be tracked. The pre-determined threshold is ≥ 50%.

2.6.2.4. Measurement completion. Measurement completion rate, defined as the percentage of completed measures (PROs, functional fitness, objective physical activity levels) will be tracked. The pre-determined measurement completion is ≥ 60% for pre- and post-intervention assessments, and ≥40% at the two follow-ups (6 and 12 months).

2.6.2.5. Adverse events. To assess the safety of the intervention, all adverse events will be tracked and reported using a standardized adverse event reporting form, that ranks events as level 1 (minor incident with no lost time beyond day of injury; temporary, immediate care), level 2 (medical aid with no lost time beyond day of injury; medical care beyond first aid), and level 3 (serious injury or death).

2.6.3. Secondary outcome: preliminary effectiveness

To examine the preliminary effectiveness of the exercise intervention, PROs and assessments of functional fitness will be conducted. All measures were chosen based on their established validity, previous use in cancer patients, and relevance to the evaluation of the benefits of an exercise oncology program.

2.6.3.1. Patient-reported outcomes. Patient-reported outcomes (PROs) will include symptom burden, physical activity levels, quality of life, cognitive function, and fatigue. Symptom burden will be assessed using the revised Edmonton Symptom Assessment System (ESAS-r), which evaluates nine common symptoms experienced by cancer patients [29, 30]. Self-reported exercise levels will be assessed using the modified Godin Leisure-Time Exercise Questionnaire (GLTEQ) [31] which reports mild, moderate, vigorous intensity and aerobic, resistance, and flexibility activities that last more than 10 min. Quality of life will be assessed using the Functional Assessment of Cancer Therapy-Brain (FACT-Br), which includes subscales for physical well-being, social/family well-being, emotional well-being, functional well-being, and additional neuro-oncology specific concerns, such as reporting seizures, speech difficulties, memory, etc. [32]. Cognition will be assessed using Functional Assessment of Cancer Therapy-Cognition (FACT-Cog), which includes subscales for perceived cognitive impairments [33]. Fatigue will be assessed using the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACT-F) [34]. Finally, physical activity preferences will be collected from participants at baseline to help tailor their individual exercise prescription.

2.6.3.2. Assessment of functional fitness. Assessments of functional fitness will follow the set protocols within the larger ACE study [18], and are designed to be able to be completed in-person or via remote delivery (online assessment). All fitness assessments will be completed by an exercise specialist and will include assessments of body composition, muscular strength, muscular endurance, balance, flexibility, and cardiorespiratory fitness. Given the online nature for the start of ACE-Neuro, only the online assessments are indicated here. See Supplementary File 1 for a table of the in-person assessments. For online assessments, resting heart rate will be measured by the study-provided activity tracker or via manual palpation. Resting blood pressure will be measured if the participant has an at-home blood pressure monitor. Participants’ height and weight measurements from the triage clinic (Calgary) or their most recent medical appointment (Edmonton) will be used. Muscular endurance will be measured by the 30 s sit-to-stand test [35,36]. Static balance will be measured by the single-leg-stance following the Canadian Society for Exercise Physiology (CSEP) protocol [37,38]. Flexibility will be measured using the sit and reach test [39, 40] and the shoulder flexion test [41]. Cardiorespiratory fitness will be measured using the 2-Minute Step Test [42].

2.6.3.3. Objective physical activity. Objective physical activity will be measured via the use of a consumer-level wrist-worn activity tracker (WAT; i.e., Garmin Vivofit 4). Garmin wearable activity trackers have high inter-device reliability of step count and are widely used across health research [43]. The Garmin activity tracker will be provided to all participants to objectively track physical activity habits throughout the intervention. Total weekly steps and physical activity minutes (i.e., mild, moderate, vigorous) will be tracked between baseline and week 12 of the program.

2.6.3.4. Qualitative interviews and photo elicitation. Qualitative data will be gathered across the study timeline via interviews and photo elicitation [44], to inform the feasibility of ACE-Neuro, as well as to assess outcomes associated with participation in the ACE-Neuro program (i.e., benefits, barriers, satisfaction, impact on well-being, impact on sense of self). All participants and their caregivers will be invited to a 45-60 min post-program interview, which will be recorded using [1]: a voice recorder if in-person or [2] end-to-end encrypted Zoom if remote. Participants will be interviewed within 2 weeks of completing the 12-week exercise program to limit recall bias, allowing them to reflect on their experience in the program. The interview guide is informed by the COM-B behaviour change framework examining participant capabilities, opportunities, motivations, and behaviour [24]. All healthcare providers and administrators involved in this work will also be invited for an interview to understand their clinical perspectives of ACE-Neuro implementation. The qualitative phase of this study will be guided by an interpretive description methodology and constructivist philosophy [45]. Interpretive description is well-established and has been used to guide numerous health-disciplined qualitative papers [46–51]. With consent, patients who engage in this process will have candid photographs taken, and/or will be encouraged to take photos of their journey via their mobile device/personal camera, or a study-provided disposable camera. Standardized instructions for capturing photos will be provided to participants. Photos will be sent to the study team via the secure, end-to-end encrypted messaging app, Signal (https://signal.org/). When
available, photos will be presented to the patient during the interviews to elicit memories and feelings. This can be a powerful tool to reinforce the nature of their exercise oncology program experience, and is a valid tool for aiding more in-depth understanding of the patient experience [44]. Photos gathered from and/or taken of patients will be transferred from the Signal App, study-provided disposable camera, or from the study team and stored on a secure University of Calgary server.

2.7. Statistical analysis

2.7.1. Quantitative data
Descriptive characteristics of participants will be presented as mean ± standard deviation or percentages. Feasibility will be reported descriptively in relation to the pre-determined thresholds. We will investigate preliminary effectiveness of our secondary outcomes. Descriptive statistics will also be reported for feasibility numbers, PROs, functional fitness, and objective physical activity. Change scores will be calculated for PROs and functional fitness and to calculate power for a future fully-powered trial. Where available, the minimum clinically important difference (MCID) [52] will be reported as an indicator of clinical significance, which is appropriate for a pilot study.

2.7.2. Qualitative data
Interviews will be transcribed verbatim via ExpressScribe and coded in NVivo 12. As per an interpretive description methodology, the data will be inductively analyzed by two independent authors who will generate themes from the codes, followed by critical feedback from experts in qualitative research and exercise oncology.

3. Discussion

The purpose of this pilot study is to assess the feasibility of a tailored exercise oncology program, ACE-Neuro, for individuals with primary brain tumours. The primary outcome of this study is to determine the feasibility of referral, enrolment, program adherence, measurement completion, and adverse events. The secondary outcomes include examining preliminary effectiveness of the neuro-oncology exercise program on patient-reported outcomes, functional fitness, and physical activity levels.

While exercise oncology programming is available for all tumour groups, patients with primary brain tumours remain underrepresented in the research process and underserved in exercise resources. By delivering one-on-one sessions, we hope this work will provide additional opportunities to participants that may have struggled in group-based settings that did not fully address their needs.

Findings from this work will be disseminated through academic channels (e.g., manuscripts, presentations), as well as through non-academic leveraging (e.g., knowledge translation initiatives such as patient group presentations, online resources for patients). Using an implementation framework approach (i.e., the RE-AIM framework; Reach, Effectiveness, Adoption, Implementation, Maintenance) [53], findings will target existing programs to improve resources, program delivery, and fine-tune models of care [54].

3.1. Limitations
First, due to the smaller population of neuro-oncology patients, we may not have the power to determine effectiveness of the intervention on secondary outcomes (i.e., PROs, functional fitness). Instead, the feasibility and preliminary effectiveness findings of this study will be used to calculate the power for a future exercise trial in this population. Second, due to COVID-19, the delivery of our programming will initially be offered online, with the option of returning to in-person delivery once restrictions lift. Depending on participant preferences, we will continue to offer both options throughout the study duration. With the transition from online to in-person ACE-Neuro program delivery, we risk inconsistency in the results of our assessment of functional fitness. Nevertheless, the assessments that have been chosen can be replicated in both online and in-person settings with the same protocol in place.

Finally, due to the advanced nature of a brain tumour diagnosis and its associated treatments and side effects, it is important to note that some patients may not complete the full study intervention and measures, leading to lower adherence rates and poorer outcomes.

4. Conclusion

Patients with primary brain tumours are a clinically underserved patient population that are underrepresented in the exercise oncology research. To address this gap, ACE-Neuro is a tailored exercise oncology program that will be implemented into the clinical care pathway across Alberta. ACE-Neuro provides an opportunity to provide patient-centered supportive cancer care that enhances wellness for individuals living with a brain tumour diagnosis.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Study registration

This study was pre-registered at ClinicalTrials.Gov. Clinical Trials Registration Number: NCT04831190 (https://clinicaltrials.gov/ct2/show/NCT04831190).

Author contributions

Conceptualization: JTD, LCC, GRU, MHM, NCR; Data curation: JTD; Funding acquisition: NCR; Investigation: JTD, LCC, MLM, NCR; Methodology: JTD, LCC, GRU, MHM, JCE, MLM, GFJ; Project administration: JTD, NCR; Resources: MLM, MdGW, NCR; Supervision; NCR Validation: JTD, NCR; Visualization: JTD, NCR; Roles/Writing - original draft: JTD, NCR; Writing - review & editing: JTD, LCC, GRU, MHM, JCE, MLM, GFJ, TW, JD, EM, PAO, MdGW, LR, AD, CL, NCR.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.conctc.2022.100925.

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