Clinical and cost-effectiveness of Cancer Patients' Needs Assessment in Primary Care (CANAssess2): A pragmatic cluster randomised controlled trial

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#See appendix-p35-37 for all Collaborative members

SUMMARY

Background

The Needs Assessment Tool-Cancer (NAT-C) is a consultation guide to identify and triage patients' and carers' unmet needs. Its effectiveness in primary care is unknown.

Methods

Pragmatic, unblinded cluster randomised controlled trial comparing clinical and cost-effectiveness of the NAT-C in primary care *versus* usual care (UC) in adults with cancer in England. Eligible general practices (willing to be trained and deliver NAT-C; practice-level consent) were randomly assigned (minimisation, 1:1, stratified by size, locality, training status) to deliver a NAT-C consultation plus UC, or UC alone. Eligible patients (≥18 years, cancer – any stage, not in remission) and carers (family or friend nominated by patient) consented to complete questionnaires at baseline, 1, 3, and 6-months and attend a NAT-C appointment if registered with an intervention practice. Primary outcome was at least one moderate-severe unmet need at 3-months (Supportive Care Needs Survey Short Form 34 [SCNS-34]). Secondary outcomes included at least one moderate-severe unmet need at 1- and 6-months; and at all timepoints: level of unmet needs (SCNS-34 score), symptoms (ESAS-r), quality of life (EQ-5D-5L, EORTC QLQ-C15-PAL), performance status (AKPS), carers' ability to care and well-being. Effectiveness analyses were according to intention-to-treat. The original sample size target of 1080 participants across 54 practices was reduced in a protocol amendment to 950 across at least 38 practices due to recruitment challenges and improved retention. Registration: ISRCTN15497400.

Findings

Between December 1st 2020 and August 31st 2023, 788 participants (mean age 66.9 years; 98.6% white; 48.7% male; 42.2% advanced disease) and 249 carers were recruited from 41 practices; 376 in 21 NAT-C, 412 in 20 UC. Follow up was complete by December 2023. Intention-to-treat 3-month primary outcome analysis showed no evidence of benefit (149/321 [46.4%] NAT-C vs 173/364 [47.5%] UC; adjusted odds ratio (OR) 0.98 [95%CI 0.63, 1.53],p=0.9428). There was no evidence of benefit for any outcome at one or three months. However, there was evidence of benefit in the NAT-C arm on secondary 6-month level of unmet needs (adjusted mean difference [MD] -3.57 [95%CI -6.57,-0.58],p=0.0195; predominantly psychological and physical needs),

symptoms (ESAS-r MD -2.98 [95%CI -5.35,-0.61],p=0.014) and QoL (EORTC QoL MD 3.97 [95%CI 1.03, 6.91],p=0.0082). There was no evidence of benefit for other 6-month outcomes of at least one moderate-severe unmet need (OR 0.66 [95%CI 0.42, 1.04], p=0.075), performance status (MD -0.02 [95%CI -2.22, 2.17], p=0.98), or carers' ability to care (MD -0.06 [95%CI -4.21, 4.09], p=0.98) and well-being (MD 0.00 [95%CI -1.90, 1.90], p=0.99).

Interpretation

In this large primary care RCT, we found no evidence of benefit at the 3-month primary endpoint timepoint, however, our data suggest some potential benefits for patients at 6 months, although future studies with longer follow up will be needed to clarify these findings.

Funding

Yorkshire Cancer Research.

PANEL: RESEARCH IN CONTEXT

Evidence before this study

We searched Medline (January 2000 – June 2024) but found no randomised controlled trials (RCTs) evaluating cancer holistic needs assessments regarding patient-reported outcomes in primary care.

Johnstone and colleagues' systematic review of holistic cancer needs assessment (HNA) tools found four secondary care-based RCTs with patient-reported outcomes. Findings were mixed, but full screening of needs with triage appeared most beneficial. Carey and colleagues' systematic review of interventions to reduce cancer-related unmet need, found 3/9 RCTs/quasi-RCTs (one UK; none in primary care) showed some benefit, mainly in psychological outcomes. The only RCT (oncology setting; UK) of the Macmillan HNA tool showed no difference in outcomes.

We adapted and validated a clinician consultation guide (Needs Assessment Tool – Cancer [NAT-C]) for UK primary care. The subsequent non-controlled feasibility study showed a larger trial was feasible and a promising inreduction in unmet need.

Added value of the study

Patient-reported benefit from HNA interventions has been difficult to demonstrate in RCTs. This study is the first Phase III clinical- and cost-effectiveness RCT of a validated primary care intervention which, despite finding no difference at one month or our primary 3-month outcome, provides evidence of patient-reported benefits across physical and psycho-social domains (consistent with an holistic intervention) at 6-months. Given these benefits are seen in *secondary* outcomes at a single timepoint, these findings should be viewed as suggesting benefit and further research, including longer term repeated follow-up trials are needed.

Implications of all the available evidence

Our novel (to our knowledge) findings – amalgamated with other RCTs in secondary care settings, quality improvement evaluations in primary care and no evidence of harms, - suggest the NAT-C might support a systematic and cost-effective needs assessment approach in primary care, standardise a current lottery of practice and be added to policy recommendations. These

secondary outcome findings, however, requires further research to confirm or refute our findings. We welcome future real-world evaluations or replication featuring a 6-month primary outcome, extended repeated follow-up, and a pragmatic design to strengthen 'real-world' relevance and implementability.

MAIN TEXT

INTRODUCTION

Over three million people live with cancer in England; expected to rise to 4 million by 2030(1). Reported levels of unmet need range from 24% to 88%, more in those recently diagnosed, with metastatic disease or at the end of life(2). However, despite policy directives such as the NHS Cancer Plan(3), aiming to improve care with a role for primary care, this situation remains unchanged(4). In 2003, cancer care review consultation post-cancer diagnosis were introduced in UK primary care. This attracts a fee for service(5) and although most general practices provide reviews, these vary from a call to a holistic needs assessment (HNA). Despite UK-wide adoption of cancer care reviews, a systematic review (10 articles; small surveys, service evaluations, interview studies, no RCTs) found little evidence of clinical benefit(6). Although some value could be seen qualitatively, patients interviewed couldn't remember having a review, or felt it to be of little value, and clinicians felt too time-pressured to complete effectively.

Other approaches, such as HNAs and cancer survivorship plans, are mostly used in secondary care (e.g., oncology out-patients) with little evidence of clinical benefits - as distinct from process measures(7-10).

The Needs Assessment Tool-Cancer (NAT-C) is a clinical consultation guide adapted and validated for UK primary care(11) which demonstrated a promising reduction in unmet need in our non-controlled feasibility study(12). The CANAssess2 trial aimed to evaluate the effectiveness and cost-effectiveness of the NAT-C in reducing patient unmet need and other outcomes and reducing carer burden in primary care.

METHODS

Study Design

The CANAssess2 (Cancer Patients' Needs Assessment in Primary Care) trial was a pragmatic two-arm parallel-group multicentre cluster-randomised control trial of the NAT-C *versus* usual care (UC) in patients with active cancer. Our methods, informed by a feasibility trial(12), are detailed elsewhere(13). The primary endpoint was at 3-months. Participants recruited up to June

1st 2023 were followed-up at 1-, 3-, and 6-months after recruitment. From June 2nd 2023 they were followed-up at 1-, and 3-months only. A 12-month internal pilot assessed recruitment, intervention uptake and follow-up. An economic evaluation of within-study cost-effectiveness is summarised here, but details and an embedded process evaluation exploring issues relating to implementation will be reported elsewhere. Patient and public involvement representatives were involved throughout, contributing to trial design, documentation, conduct, oversight and outputs.

CANAssess2 was conducted across Northeast England and Yorkshire. The protocol and subsequent amendments (Appendix-p3-4) were approved by London-Surrey Research Ethics Committee (20/LO/0312). The trial was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki and registered (ISRCTN15497400).

Protocol amendments (Appendix-p3-4) were made to allow the trial to be run fully remotely (protocol v3.0, approved July 24th 2020) and reduce the sample size to 950 participants across a minimum of 38 general practices (protocol v8.0, approved September 20th 2022) due to the COVID-19 pandemic. A protocol amendment was also made to allow practices to take part regardless of their use of other needs assessment tools (protocol v7.0, approved February 28th 2022).

Participants

General practices were recruited through the regional Clinical Research Network (now Research Delivery Service). Eligible general practices (Appendix-p5) were willing to be trained and deliver the NAT-C for recruited patients if so allocated; were willing to commit to trial procedures; and gave written informed practice-level consent.

Eligible patients (Appendix-p5) were consenting (written or observed verbal) adults (≥18 years) with active cancer (i.e. receiving anti-cancer treatment with curative or palliative intent; managed with “watch and wait”; recurrent or metastatic). Patients were excluded if they were: living in an institutional setting; within one month of cancer diagnosis; had basal cell carcinoma only; in complete remission. Eligible carers were patient-nominated, consenting adults aged 18 or over (family or friend), supporting the patient. Patients and carers needed sufficient English to contribute to data collection (with interpreter if needed).

Patients on the practice cancer register were screened by a practice clinician and eligible patients were sent a trial invitation letter, opportunistically recruited through routine clinical contact, or identified from the Gold Standards Framework practice list.

Randomisation and masking

Practices were randomly assigned (1:1) to deliver the NAT-C intervention or UC alone. Allocation, via a web randomisation system at the University of Leeds Clinical Trials Research Unit, used minimisation incorporating a random element to ensure treatment groups were well balanced for strata: list size (small [<5,000]/medium [5,000–10,000]/large [>10,000]) locality (urban/rural area and training centre status (yes/no).

General practices and research nurses providing recruitment and follow-up support were aware of treatment allocation. Screening logs and baseline characteristics were monitored for selection bias. Participants were masked to the intervention details but not practice allocation (participants were informed that those registered with intervention practices would be invited to attend an appointment with a clinician and that those registered with a control practice would not). Analysts were unblinded.

Procedures

In each intervention practice at least one clinician was trained online (JC, TMc) to use the NAT-C using a one-hour training package piloted during feasibility work. Intervention participants were invited by the practice to attend an approximately 20-minute NAT-C guided consultation with a trained clinician within two weeks of study registration at the practice, patients' homes or remotely according to clinical judgement.

The NAT-C is a one-page psychometrically valid, reliable, and clinically acceptable tool for assessment of patients' and carers' holistic needs(11). It differentiates between need addressable by the UC team and that requiring referral to other services, e.g. palliative care, psychology, benefits advice. Resulting clinical action was according to individual clinician judgement and patient or carer agreement. Carers were welcome to accompany patients, however, the NAT-C allows patient-proxy assessment of carer need. The NAT-C was completed using the electronic medical record (EMR) template, or on paper and uploaded to the medical record.

Control practices were asked to continue UC, defined as the management normally provided in accordance with the General Medical Services contract(14). There were no limitations on other treatments received simultaneously.

Participants completed questionnaires (electronic, postal, phone, face-to-face as appropriate, including validated outcome measures and health care resource use) at baseline, 1-, 3-, and 6-

months post-registration. Researchers phoned participants to confirm questionnaire receipt and collect the Australia-modified Karnofsky Performance Score (AKPS(15)) and COVID-19 status (and baseline demographics, Table-1). Non-responders were sent email or postal reminders after two weeks and phoned by a researcher after three weeks.

We documented serious adverse events fulfilling the definition of a related unexpected serious adverse event (RUSAE, identified via researcher contact or direct participant report), and the date and cause of all deaths occurring during the trial period were collected from medical records.

Data on participant level UC were collected across trial arms from health resource use questionnaires and from the medical record for receipt of other holistic reviews. We recorded the use of needs assessment tools at participating practices before recruitment and after follow-up to monitor changes in usual care.

Outcomes

The primary outcome was at least one moderate-severe unmet need (Supportive Care Needs Survey Short Form 34(16) [SCNS-SF34]) at 3-months. The level of unmet need overall across all five domains of the SCNS-SF34 (i.e., continuous score) at 3-months was measured as a secondary outcome.

Other secondary patient outcomes included at least one moderate-severe unmet need and the level of unmet needs (SCNS-SF34) at 1- and 6-months, the level of domain-specific (Psychological, Health Systems, Physical Care, Sexual) unmet needs (SCNS-SF34), performance status (AKPS)(15), severity of symptoms (Revised Edmonton Symptom Assessment System, ESAS-r)(17), mood and quality of life (QoL)(European Organisation for Research and Treatment of Cancer Quality of Life-C15-Palliative questionnaire, EORTC QLQ-C15-PAL)(18) at 1-, 3-, and 6-months.

Carer outcomes included ability to care from the Carer Experience Survey (CES)(19) and wellbeing from the Zarit Burden Interview (ZBI-12)(20) at 1-, 3-, and 6-months.

Health economic measures included the EQ-5D-5L(21) and EQ-VAS, ICEpop CAPability Supportive Care Measure (ICECAP-SCM)(22), and health resource use at 1-, 3-, and 6-months.

Additional process outcomes to evaluate intervention delivery, uptake and fidelity of the NAT-C included: number of NAT-C trained clinicians in each general practice, completed NAT-C consultations, length of NAT-C consultations, referral patterns and actions to meet identified unmet need from the completed NAT-C.

Statistical Analysis

We estimated a sample size of 1080 participants from 54 practices would provide 85% power with two-sided 5% significance level to detect a relative difference of 22% in the proportion of patients with at least one moderate-severe unmet need at 3-months (14% absolute difference, 64% to 50%)(23). Calculations assumed 20% loss to follow-up, 0·05 intra-cluster correlation coefficient (ICC), and average cluster size of 20 (range 4-40). Due to COVID-19 related recruitment challenges, but improved 10% loss to follow-up, the sample size was reduced to 950 participants across a minimum of 38 general practices (increased average cluster size 25, smaller range 10-40, same ICC 0.05; Appendix-p3-4) to provide 80% power with 5% significance level to detect the same 22% relative difference in the proportion of patients with an unmet need. Subsequently, in discussion with the Trial Steering Committee and after recruitment of 41 practices (exceeding the revised target of 38, and with reduced anticipated average cluster size 21, smaller range 10-35), we informally re-estimated sample size requirements to retain 80% power as 850 participants.

All statistical testing used two-sided 5% significance levels, performed in SAS, version 9·4 or R version 4.4.1, and were prespecified unless indicated. We undertook single final analysis of outcomes data (including internal pilot data). Primary effectiveness analyses was according to the intention-to-treat population, defined as all participants recruited and according to their practice allocation, regardless of adherence. We assessed selection bias *via* statistical testing of baseline participant data.

We compared between-group outcome measures using a two-level hierarchical generalized logistic or linear (appropriate to outcome) mixed model with repeated measures and participants nested within practices (participant and practice random effects; AR(1) covariance structure). Pre-specified fixed effects included treatment group, time, treatment-by-time interaction; practice randomisation strata; participant age, sex, cancer status, baseline measure of the dependent variable (for continuous outcomes) and AKPS. EORTC QLQ-C15-PAL physical subscale was also included as a fixed covariate as identified as predictive of missingness (a pre-specified approach to exploration and handling of missing data). Results were expressed as adjusted odds ratios (OR, NAT-C/UC) or mean differences (MD, NAT-C - UC) with 95% confidence intervals (CI), p-values, and ICCs for the 3-month primary endpoint and secondary endpoint level of unmet need. Assumptions were checked for all models using Pearson and Studentised residual plots.

We explored missing data patterns to identify participant characteristics related to missingness and differential missingness by treatment group (Appendix-p15). Primary analyses

took a missing at random approach, including all participants with at least one post-baseline measurement(24). We treated data truncated due to death as for missing data, adopting a treatment policy estimand strategy(25). Sensitivity analyses on the primary endpoint and secondary endpoint of level of unmet need used: multiple imputation unadjusted models (excluding covariates), separate analyses per timepoint, analysis restricted to the 6-month follow-up population, and included carer covariate (post-hoc).

We summarised intervention delivery, receipt of UC, deaths (including Kaplan-Meier Survival Estimates), and RUSAEs descriptively only.

Exploratory moderator analyses of the primary endpoint and secondary endpoint of level of unmet need investigated whether the treatment effect varied by practice and participant-level variables, using a treatment-moderator interaction in separate analysis at each timepoint. Further exploratory analysis examined the impact of intervention compliance using a complier average causal effect (CACE) and per-protocol analyses (excluding protocol violations and deviations, Appendix-p10).

The economic evaluation was a cost-utility analysis over the 3- and 6-month time horizon from a health and personal social services perspective using standard UK national unit costs. Intervention delivery costs, including training costs and time for delivery, were included. Survival was adjusted to create quality-adjusted life years (QALYs) using the EQ-5D-5L, with utility values derived using the UK crosswalk value set(21) and QALYs via the area-under-the-curve. QALYs and costs were estimated in models using the same covariates as the statistical analysis along with baseline costs and EQ-5D-5L, applying separate linear (QALYs) and generalised linear (costs) models (primary analysis) and linear, seemingly unrelated regression (secondary analysis). We derived incremental cost-effectiveness ratios (ICER) and/or incremental net monetary benefit (incremental QALYs*threshold-incremental costs) to compare cost-effectiveness of the NAT-C to usual care. A £20,000 threshold per QALY gain was assumed. Complete case primary analysis is provided, supported by exploration of missing data patterns and sensitivity analyses using multiple imputation to assess stability of findings. Cost-effectiveness uncertainty was explored through non-parametric bootstrapping and cost-effectiveness acceptability curves. Full methods and more detailed health economic analysis will be reported separately.

Given the nature of the intervention, lack of blinded data and a low-risk trial, the Trial Steering

Committee adopted a safety data monitoring role with the agreement of Sponsor and Funder.

Role of the funding source

The study funder (Yorkshire Cancer Research: H423) had no role in study design, data collection, analysis, interpretation, or manuscript preparation.

Results

Of 65 general practices expressing interest, 41 were randomised and opened to recruitment between October 21, 2020 and April 12, 2023: 21/41 (51%) in the NAT-C and 20/41 (49%) in the UC arm (Figure-1). An additional practice was randomised to NAT-C but withdrew prior to recruitment. Between December 1, 2020 and August 30, 2023, 2,874 patients were screened (practice cancer registry search except for 39 opportunistic approaches, Appendix-p6), of whom 788 (mean age 66.9 years [SD 10.9]; 51% female; 58% early localised cancer *versus* advanced localised or metastatic; ≥1 comorbidity; ≥1moderate-severe unmet need) were enrolled: 376/788 (48%) in the NAT-C arm, and 412/788 (52%) in UC. Over half identified a carer (427/788, 54%), and a carer was recruited alongside 249/788 (32%) participants, slightly more in the NAT-C arm (Table-1, Appendix-p8).

Practice-level strata were well-balanced (Table-1); most were urban, training practices, and around half had a medium list size. Participants were representative of screened patients in terms of age, sex, and registration on the Gold Standard Framework (a register of patients considered to be end-of-life, Appendix-p6). Almost all screened and recruited participants were white (Table-2). Participants were recruited a median 21.9 months (range 1-332) after their initial cancer diagnosis. There was no evidence of selection bias, except for increased presence and recruitment of a carer in NAT-C participants (Tables 1-3). At baseline, over a quarter of participants felt that their cancer care had worsened due to the COVID-19 pandemic; 31% had tested positive previously increasing to 40% by the end of follow-up (Appendix-p9).

Follow-up completed in December 2023. At least one post-baseline questionnaire was returned for 742/788 (94%) participants, primary 3-month follow-up was completed for 692/788 (88%) and 6 months (where applicable) for 583/669 (87%), with similar rates across arms (Figure-1,Table-3). Participants recruited with follow-up limited to 3-months (n=119) had higher baseline levels of unmet need (Appendix-p19). Participants missing 3-month primary outcome data had

less favourable characteristics across multiple baseline measures, predominantly physical functioning (thereby included as an analysis covariate, Appendix-p15-18); there was no evidence of differential patterns by arm apart from practice locality.

A total 35/788 (4%) participants and 16/249 (6%) carers withdrew consent for at least one trial process (Figure-1), and 51/788 (6%) participants died (20 within 6-months; Figure-1 Appendix-p10-11). Major protocol violations occurred in five (<1%) participants (Appendix-p10). There were no RUSAEs.

We trained 54 clinicians to use the NAT-C, which was delivered to 360/376 (96%) participants in the NAT-C arm (Appendix-p12). Most consultations were completed within one month of recruitment (median 13 days, IQR 7-22), by telephone (229/347, 66%), and without a carer present (279/316, 88%). Consultations took a median 24 minutes (IQR 20-30) and led to external referrals for 50/360 (14%) participants; mostly to specialist palliative care (n=10) or psychology (n=7). Action was taken for 258/360 (72%) participants, with direct management of at least one need for 232/360 (64%) participants and management by another team member for 61/360 (17%) participants (Appendix-p13).

Receipt of other cancer care reviews or HNAs within UC were identified for 221/788 (28%) participants since their diagnosis and up to 6-months post-registration (84/376, 22% in NAT-C; 137/412, 33% in UC); most were other primary care reviews, and some using other electronic health record templates(26, 27) (Appendix-p14). Only 47/788 (6%) participants had such assessment during the 6-month trial period (26/376, 7% in NAT-C; 21/412, 5% in UC).

For the 3-month primary outcome, 149/321 (46%) participants in the NAT-C arm and 173/364 (48%) in UC reported at least one moderate-severe unmet need (Table-2). The OR 0·98 (95% CI 0·63 to 1·53, p=0·94, ICC 0.067) of unmet need in NAT-C versus UC provided no evidence that NAT-C was superior to UC (Appendix-p19,21). Similarly, we found no evidence that NAT-C was superior to UC in reducing the level of unmet need (MD -0·51, 95% CI -3·36 to 2·35, p=0·73; ICC 0.043; Table-2, Appendix-p20,22).

At 6-months however, there was weak evidence that the NAT-C was superior to UC at reducing the proportion of individuals with at least one moderate-severe unmet need (OR 0·66, 95% CI 0·42 to 1·04, p=0·075) and good evidence for a reduction in the level of unmet needs (MD -3·57, 95% CI -6·57 to -0·58, p=0·020).

There was no change in conclusions from sensitivity or exploratory analysis of the 3-month primary-endpoint (Appendix-p21-22). At 6-months, CACE and sensitivity analyses using multiple

imputation and separate analysis at each timepoint resulted in more precise confidence intervals, suggesting good evidence for a beneficial 6-month effect. Higher baseline unmet needs, advanced cancer, worse performance status and physical functioning were predictive of higher likelihood and level of unmet need at follow-up; there was weak evidence that being male was predictive of higher levels of unmet need (but not of any unmet need, Appendix-p23,29).

Other secondary outcomes (Table-3, Appendix-p24-29) were largely similar, with no evidence of a difference on outcomes at 1- or 3-months, but good evidence in favour of the NAT-C at 6-months on unmet psychological and physical needs, severity of symptoms (pain, appetite loss), QoL, and emotional functioning. There was no evidence of a difference on other patient- or carer-participant secondary outcomes at 6-months.

Exploratory sub-group analyses found limited evidence of a differential treatment effect on 3- and 6-month primary and key secondary outcomes (Appendix-p30-33), with the exception of an increased benefit of the NAT-C on the level of unmet need at 6- but not 3-months in patients not on the Gold Standard Framework (interaction p=0.033) and patients with higher baseline levels of unmet need (interaction p=0.043).

Complete case (n=644) economic analyses (descriptive summaries in Appendix-p34) estimated mean incremental QALYs and costs [incremental net monetary benefit; INMB] for NAT-C versus UC at 3-months at 0.006 (95%CI -0.013 to 0.025) and -£212 (95% CI -£1213 to £789)[£332]; and 0.015 (95% CI -0.027 to 0.058) and -£283 (95% CI -£1607 to £1040)[£583] at 6-months. At both timepoints, estimates indicated that NAT-C was both cost saving and provided QALY gains compared to UC; however, the wide confidence intervals crossing zero for both costs and QALYs mean that we cannot draw firm conclusions about cost-effectiveness. For the complete case sample, using linear, seemingly unrelated models, the probability that NAT-C was cost effective was over 0.80 at 3- and 6-months, although this was sensitive to analytical approach. In multiply imputed analysis, 3-month mean QALY differences were 0.001 or 0.004 (depending on the model) while mean cost differences were -£168 or £322[INMB £-302-£248]; 6-months, mean QALY differences were 0.001 or 0.05 while mean cost differences were -£194 or £308[INMB £206-£692]. Thus, NAT-C was either dominant (cheaper and more effective) or more effective but more expensive (not cost-effective) depending on the modelling approach.

DISCUSSION

We found no evidence of benefit at 1-, or the primary 3-month endpoint. However, we found,

for the first time to our knowledge, evidence of patient-relevant benefit at 6-months on secondary outcomes of overall level of unmet need, psychological and physical unmet need, symptom severity (pain, appetite), QoL, and emotional functioning. While point estimates favoured NAT-C in terms of QALYs and costs, imputed analyses showed greater variability, with cost-effectiveness conclusions sensitive to the model used. There were no RUSAEs. There was high intervention compliance with consultations lasting, on average, approximately twice the length of a routine appointment. Although we did not reach our target sample size, the negligible difference observed at 1- and 3-months suggest that increased statistical power would not have altered our conclusions. However, greater power would have reinforced the strength of evidence for the beneficial effect observed at 6 months.

Despite the prevalence and impact of unmet need in people with cancer, clinical effectiveness evidence for interventions is lacking(4), particularly in primary care settings. Holistic assessment approaches are recommended in the UK (e.g., holistic needs assessment, cancer care reviews) and other mainly high-income countries (e.g., survivorship care plans). The challenges of demonstrating clinical benefit are highlighted in a systematic review of survivorship care plans(10). Only 'proximal' outcomes (directly resulting from the care plan)(10) such as patient satisfaction showed benefit. The more 'distal' (requiring a chain of actions) patient-reported benefit outcomes take longer to show benefit (e.g., from changing medications, referrals). This is consistent with our finding of benefit but not until 6 months, and of others; benefits tend to occur after such a period(9).

Another potential explanation for the 'delayed' effect relates to systematic holistic enquiry and the message to the patient legitimising their concerns(28). To *volunteer* concerns, a patient needs health literacy and agency to recognise their concern as something potentially remediable and that the clinician is the right person to tell. Given the relationship between social determinants of poor health and poor health literacy(29), relying on patients to volunteer concerns builds in inequity. Further, patients consider doctors to have little time, and a perception of a 'one problem, one appointment rule' forces patients to prioritise their most pressing issue - at least in the UK standard 10-minute appointment(30). More unmet needs are identified using systematic enquiry. One palliative care study showed that patients, on average, *volunteered* one concern but disclosed ten with systematic enquiry; all considered serious by the

patient. In another study of women with breast cancer, the number of concerns using a patient-completed holistic needs tool were greater than those extracted from clinical case records(31). In our feasibility study, clinicians interviewed were concerned that a systematic approach will identify needs that they cannot address(5). However, the patient interviews identified that the NAT-C guided consultation made them feel 'seen and heard'; they did not expect resolution of all issues, and acknowledgement was helpful(5). Potential concerns that increased primary care input may further fragment care were not confirmed, rather, patients felt reassured that their primary care team was aware of their situation and signposted appropriately(5).

CANAssess2 had strengths and limitations. The trial took place across a wide area of northern England with diverse populations increasing the generalisability of our findings. Participants represented different cancer types and stages, and co-morbidities. However, we did not collect data on race, and minoritised ethnic communities were under-represented, a group who may have higher levels of unmet need, limiting generalisability. Our patient population was healthier compared with our feasibility study. Recruitment of a population with more unmet needs may have provided greater scope for benefit. This is supported by our exploratory subgroup findings at 6-months, which showed stronger beneficial treatment effects in participants with a greater baseline level of unmet need. However, the absence of a difference in outcomes at 3 months was consistent across all baseline levels of unmet need.

Participant recruitment occurred after practice-randomisation, but we found no evidence of selection bias, except for a higher proportion of participants in the NAT-C arm having a carer. However, this did not affect the primary results. Inevitably, participants were unblinded to allocation. We minimised potential risk of self-selection bias and in outcome measurement by: masking potential participants to the details of the intervention at trial enrolment; ensuring clinical care providers were not involved in data collection; and using standardised outcome assessment methods and follow-up processes across trial arms. The success of which is illustrated *via* comparable recruitment and follow-up rates across trial arms. It is possible that questionnaire completion may have triggered help-seeking behaviour. There appears to be more access to community-based or out-patient hospital services in the control arm which might indicate this. Given previous work indicating the perception of patients that the health services are overwhelmed – especially during the COVID pandemic – we suspect such a response is unlikely.

However, if this was the case, such a Hawthorne effect could have *underestimated* any benefit seen from our intervention. Receipt of a cancer review of some sort within UC may have diluted benefit. In our sensitivity analyses, at 6-months we found a similar (non-significant) effect in per-protocol analyses, and good evidence for a smaller benefit of the NAT-C in CACE analyses.

Whilst we had missing data for just over 10% on the primary 3-month outcome and those with missing data had less favourable baseline characteristics, our analyses approach effectively reduced this to ~5% where participants had missing data across all timepoints. Sensitivity analysis, using multiple imputation, found consistent and more precise treatment effects at 6-months. There was consistent evidence of QALY gains and the potential for cost-effectiveness but substantial uncertainty around these values; highlighting the uncertainty introduced by missing data in economic analysis and a need for cautious interpretation.

Challenges in recruiting practices and participants, led to a reduced target sample size, which was ultimately not met. However, given the negligible treatment effect across 3-month outcomes, it is unlikely that increasing statistical power by meeting our sample size would have changed conclusions. Our primary outcome was binary rather than continuous, due to its use in previous trials to inform sample size assumptions(23). This approach reduces statistical power, consistent with our findings of stronger evidence of a treatment effect at 6-months in analysis of the level of unmet need compared to presence of any unmet need.

We restricted follow-up for the later enrolled participants to 3-months (primary endpoint) to reduce trial costs. This reduced the available 6-month data sample, adding complexity to analyses and interpretation. We observed some differences, particularly in baseline unmet need, between participants recruited to 3- *versus* 6-month follow-up. Participants with restricted 3-month follow-up, had higher levels of baseline unmet need. Exploratory analyses found no evidence of a differential treatment effect between these groups, but a larger 3-month benefit was observed in the 3- *versus* the 6-month cohort.

Whilst we found no differences in carer outcomes, most consultations assessed carer need using patient proxy which may have under-estimated concerns, and limited opportunities for action. Adapting the NAT-C to focus on patient need only and instead, combining with carer-faced

assessments e.g., Carer Supportive Needs Assessment Tool (CSNAT)(32), may be more effective.

The clinical importance of the findings at 6-months should be interpreted in line with available data on the minimal clinical important difference (MCID) for each outcome. However, the SCNS measure has no published MCID, and although the MCIDs are estimated to be a ≥1-point change for individual ESAS symptoms, this measure has no MCID for its summary score(17). Similarly, there is no published MCID for the EORTC QLQ-C15-PAL (chosen for its fewer items to reduce participant burden) in such a heterogeneous cancer population in the primary care setting. Although this is a limitation, we propose that the beneficial effects observed across multiple domains, and its potential translation into increased QALYs in the intervention arm, provides a rationale for further research to clarify the MCID and enable better judgement of clinical relevance.

A review of reviews of models of cancer survivorship care indicates that primary care-based models have equivalent patient outcomes, but are heterogenous, poorly adopted and face implementation barriers, and do not include people undergoing primary cancer treatment or end-of-life care(33). The authors call for implementation guidance and highlight gaps in knowledge regarding effectiveness of interventions across domains of care, understudied outcomes and differing patient populations. Although a detailed discussion regarding implementation issues is beyond the scope of this article, one hour's training and a single consultation lasting just over twice a standard 10-minute appointment appears to provide patient-relevant benefit over time in a population including all stages of active cancer. The validated NAT-C guide could be embedded into routine cancer care reviews in UK primary care helping standardise a current lottery of practice and added to policy recommendations regarding which template to use. The NAT-C could also be useful at other stages of cancer care (e.g., end of primary treatment, recurrence, advanced disease, end of life).

The NAT-C approach may have relevance beyond cancer. Many unmet needs identified may have been comorbidity-related, including those related to COVID-19 infection. A generically-adapted NAT may be useful in primary care chronic multiple disease management. Studies have, similarly to the cancer literature, not demonstrated benefit(34). However, their primary outcomes focused on QoL rather than unmet need. Of note, a quasi-experimental study of a community-based holistic assessment and management of frail older adults demonstrated benefits at 3-months using a level

of concern outcome (Integrated Palliative care Outcome Score(35)) which measures patient impact, rather than severity; a concern with a plan of action, with perceived control represents a *met* need. Future adaptation of the NAT-C for generic use and testing in combination with the CSNAT would be a good next step.

In conclusion, we found no evidence of benefit at the 3-month timepoint with the systematic use of a holistic cancer needs assessment tool. However, we found, to our knowledge for the first time, consistent statistically significant evidence of patient-relevant clinical benefit at 6-months, and potential for cost-effectiveness. However, the evidence of benefit seen in our secondary outcomes requires cautious interpretation and further research is needed to confirm or refute our findings. We welcome replication featuring a 6-month primary outcome, extended repeated follow-up, and a pragmatic design to strengthen 'real-world' relevance and implementibility, alongside future real-world evaluation.

Contributors

MJJ co-conceived and designed the trial, contributed to practice and participant enrolment, and data acquisition, and had overall responsibility in their role as chief investigator. AW-H co-designed the trial, provided statistical input into the implementation and statistical analysis plan. EMcN contributed to the protocol development, implemented the trial and contributed to the co-ordination of data acquisition and trial reporting. AH provided statistical input into the implementation and statistical analysis plan. JC co-conceived and designed the trial, contributed to the acquisition of qualitative data, and implemented the nested qualitative study. TMc, JMD, RF, and SW co-designed the trial, contributed to practice and participant enrolment, and data acquisition. JC and TMc trained intervention practices. DMM co-designed the trial; designed, implemented and supervised the health economic evaluation. JLO'D implemented the health economic evaluation. SB provided patient and public input in the implementation and trial reporting. DCC co-conceived and designed the trial. FS contributed to the acquisition of qualitative data, conducted and analysed the nested qualitative study. FD undertook operational delivery of the trial. AJF co-conceived and designed the trial, was responsible for its overall implementation across Leeds Clinical Trials Research Unit, and supervised the statistical analysis. AW-H and AH had full access to, and verified, all the data in the study. AW-H and AH had full access to, and verified, all the data in the study. EMcN and FD had access to accumulating data to support trial conduct. DMM and JLO'D accessed limited data relevant to health economic analysis. JC and FS accessed limited data relevant to the qualitative analysis. Other trial management group members did not require access to study data but could request it under the collaboration agreements. Broader access required formal data-sharing agreements. AJF is guarantor. MJJ, AW-H, AH, DMM, and JLO'D drafted the manuscript. All authors contributed to interpretation of data, commented on drafts of the paper and approved the final draft of the manuscript. MJJ, AWH, and AJF had final responsibility for the decision to submit for publication. Further contributions of authors and collaborative members are detailed in the Appendix-p35-36 according to the CRediT Taxonomy.

Data Sharing

All data requests should be submitted to CTRU-DataAccess@leeds.ac.uk and the corresponding

author for consideration. Requests would be subject to review by a subgroup of the trial team, which will include the data guarantor, Professor Amanda J Farrin and Chief Investigator Professor Miriam Johnson. Access to anonymised data could be granted following this review. All data-sharing activities would require a data-sharing agreement.

Declaration of interests

MJJ, AWH, JC, TMcC, JMD, RF, SW, DMM, AJF report AJF, AWH report payments via their institution as co-applicants on the Yorkshire Cancer Research (Grant number H423) grant supporting the present manuscript. In addition:

MJJ reports payments via their institution for grant funding from the National Institute for Health and Social Care; and unpaid contributions as independent chair of a Trial Steering Committee.

AWH reports payments via their institution for grant funding from the National Institute for Health and Social Care; unpaid contributions for independent participation on a Data Monitoring and Ethics Committee and Trial Steering Committees and as a statistical/trial design expert Committee member for the Yorkshire and North East Regional Advisory Committee for NIHR Research for Patient Benefit 08/2022 – present.

JC reports payments via their institution for grant funding from the Medical Research Council

TMcC reports Payments via their practice for the following grants or contracts: Primary Care Associate Research Lead, Yorkshire and Humber Clinical Research Network; Primary Care Regional Research Settings Co-Lead for the Yorkshire and Humber Regional Research Delivery Network.

RF reports payments via their institution for grant funding from the National Institute for Health and Social Care, consulting fees for the National Cancer Audit Collaborating Centre, and THIS Institute; and unpaid contributions for independent participation as chair on the Implementation Strategy Group and Trial Steering Committees

SW reports payments via their institution for grant funding from the National Institute for Health and Social Care

AJF reports payments via the**ir** institution for grant funding from the National Institute for Health and Social Care including and NIHR Senior Investigator award from 2021; and unpaid contributions for independent participation on a Data Monitoring and Ethics Committee, Trial Steering Committee, and programme steering committee.

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