UNIVERSITY of York

This is a repository copy of *The SCAN-ME Study Protocol:The Value of Surveillance Imaging for Children and Young People with Medulloblastoma and Ependymoma*.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/id/eprint/229910/

Other:
Shepherd, Lucy, Manca, Andrea orcid.org/0000-0001-8342-8421, Phillips, Bob orcid.org/0000-0002-4938-9673 et al. (1 more author) The SCAN-ME Study Protocol:The Value of Surveillance Imaging for Children and Young People with Medulloblastoma and Ependymoma. UNSPECIFIED. (Unpublished)

Reuse
Items deposited in White Rose Research Online are protected by copyright, with all rights reserved unless indicated otherwise. They may be downloaded and/or printed for private study, or other acts as permitted by national copyright laws. The publisher or other rights holders may allow further reproduction and re-use of the full text version. This is indicated by the licence information on the White Rose Research Online record for the item.

Takedown
If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.

White Rose university consortium
Universities of Leeds, Sheffield & York

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk/

The SCAN-ME Study Protocol: The Value of Surveillance Imaging for Children and Young People with Medulloblastoma and Ependymoma

Mrs Lucy Shepherd
Corresponding Author
NIHR Doctoral Fellow, and Research Fellow in Evidence Synthesis: lucy.shepherd@york.ac.uk (01904 321044)
Centre for Reviews and Dissemination, University of York, YO10 5DD

Professor Karl Atkin
Professor of Medical Sociology
Department of Sociology, University of York, York; YO10 5GD

Professor Andrea Manca
Professor of Health Economics
Centre for Health Economics, University of York, York; YO10 5DD

Professor Bob Phillips
Senior Clinical Honorary Consultant, Senior Lecturer in Paediatric Oncology
Centre for Reviews and Dissemination, The Hull York Medical School, University of York, York, YO10 5DD

Version Table

Version Number	***Date***	***Summary of Revisions***	***Page***
1	11/07/2023		
2	05/09/2023	- Clarified data management arrangements for audio/video recordings from interview data (Workstream 1) - Updated ethics approval statement	6 12
3	20/12/2023	- Clarification to wording relating to obtaining individual participant data (Workstream 2)	7
4	01/11/2024	- Amendments to introduction - Amendment to eligibility criteria in Workstream 1 to be aligned with ethics application approval - Amendments to individual participant data section (Workstream 2) regarding requirement to obtain additional data from patient notes for both medulloblastoma and ependymoma datasets - Additional information on data analysis provided (data analysis yet to commence) - Amendment to Workstream 3 – an economic model for the cost-effectiveness of surveillance imaging in ependymoma will not be conducted - Amendment to literature searches for Workstream 3 to number of reviewers screening records - Clarification to wording on value of information analysis	3-4 5 7 8 8-10 9 10
5	28/07/2025	- Amendment to Workstream 2 to remove use of individual participant data to determine clinical effectiveness of surveillance imaging in ependymoma due to limited data on survival.	7-8

Background

Brain and central nervous system (CNS) tumours are the second commonest cancer in children and young people (CYP), affecting around 400 individuals in Great Britain every year (1). Although survival outcomes for CYP with brain and CNS tumours has improved significantly over the past few decades, there is still variation in outcomes across tumour types, meaning they account for a disproportionate number of deaths in CYP with cancer (2, 3).

Medulloblastoma is the most common malignant brain tumour in CYP, affecting around 58 CYP in the UK every year (4). Medulloblastoma includes four different subgroups, which vary in their clinical and genetic features and in their prognosis (5, 6). Ependymomas are another type of malignant brain tumours which affect around 37 CYP in the UK every year (4). Although a greater proportion of patients with ependymoma will experience a relapse [around 50% (7)], compared to medulloblastoma [around 30% (6)] the prognosis for relapsed medulloblastoma is much worse, with less than 5% surviving, and treatments following relapse are typically non-curative (8). Patterns of relapse in ependymoma are more heterogenous: children and young people with ependymoma may experience a relatively short survival period following relapse, others experience chronically relapsing disease (9, 10).

A brain/CNS tumour relapse can be detected in two ways: either by the presence of symptoms, or asymptomatically- where a tumour is detected on an MRI scan that was administered as part of a regular schedule of follow-up appointments. Surveillance imaging aims to detect a recurrence before clinical symptoms develop, with the presumption that earlier detection of relapse will lead to improved outcomes (11-13).

The utility of surveillance imaging in medulloblastoma and ependymoma has long been debated (11, 14-16). Issues of lead-time bias (which produces a perceived improved survival when using surveillance imaging, as tumour recurrences are detected earlier) often impact the validity of the results (17). This is evidenced in study which found that although CYP with medulloblastoma whose relapse was detected symptomatically had shorter survival if measured from the point of relapse compared to those detected using MRI, overall survival when measured from primary diagnosis did not differ (18). Many studies exploring the utility of surveillance imaging in ependymoma that find significant improvement in outcomes measure survival from relapse. Given the potential impact of lead-time bias means there is uncertainty in the utility of surveillance imaging in this population (15, 19). Where survival is measured from the same point in the disease trajectory, survival – while longer in the surveillance group – was not significantly different to those whose relapse was detected by symptoms (11). Furthermore, length bias may be an issue, where the tumours detected by scans are prognostically different (slower growing in more favourable places, more amenable to be treated with local therapies) to those detected by symptoms (faster growing, disseminated, harder to treat with local therapies), meaning the efficacy of surveillance imaging can be confounded by other prognostic variables (11, 14, 20). Finally, in the case of medulloblastoma, some argue that surveillance imaging is currently futile, as an early detection of a relapse will unlikely change outcomes given the lack of curative options at second-line (14, 16).

The provision of surveillance imaging also has cost implications on health care services and resources. Despite this, there are no studies evaluating the cost-effectiveness of surveillance

imaging in CYP with medulloblastoma or ependymoma. One cost-minimisation analysis study suggested that there were no significant differences between the cost of surveillance imaging for all paediatric brain tumours and standard follow-up care. However the limited description of the methods used, and lack of consideration of quality of life or any other measurement of health benefit, mean the results are unlikely to be representative or applicable in the UK health sector and cannot inform decision makers regarding the value for money of surveillance imaging (21).

Notwithstanding, the biggest source of uncertainty-related anxiety for families was the fear of cancer recurrence (22). While surveillance imaging can reassure CYP and their families that the tumour has not recurred, it has a considerable impact on families' quality of life (23). One qualitative study found that while having scans can reassure families, and improve their sense of control, waiting for results can be a difficult and anxious time (24).

Therefore, in order for earlier asymptomatic detection of relapse to be valuable and worthwhile, it is important to weigh up the broader benefits, risks, and costs of early detection.

Methods

The SCAN-ME study has three workstreams. Each workstream of this study aims to assess the **value** of surveillance imaging for CYP with medulloblastoma and ependymoma. The objectives are:

- **Workstream 1:** To understand CYP with medulloblastoma and ependymoma and their parents' experiences and expectations of surveillance imaging.
- **Workstream 2:** To determine whether identifying an asymptomatic medulloblastoma and ependymoma relapse in CYP using surveillance imaging is clinically effective and improves overall and event-free survival following relapse.
- **Workstream 3:** To establish the cost-effectiveness of surveillance imaging compared to the use of symptomatic detection alone in CYP with medulloblastoma and ependymoma.

Workstream 1

Workstream 1 is a qualitative study which will explore the experiences and expectations of surveillance imaging for CYP with medulloblastoma and ependymoma and their parents.

Participants

CYP with medulloblastoma or ependymoma who have finished treatment, and their parents will be invited to participate in this study (see Table 1 for the eligibility criteria). To ensure the sample is reflective of families with experience of medulloblastoma or ependymoma, we will actively seek to recruit participants with a range of different familial and tumour-specific characteristics (e.g., ethnicity, socioeconomic status, age of child, tumour subgroup, requirement of general anaesthetic for the scans, and experience of tumour relapse).

Table 1. Eligibility Criteria for Workstream 1

Eligibility Criteria: Children and Young People
- Child or young person must with a diagnosis of medulloblastoma or ependymoma - Are currently receiving surveillance imaging following treatment - Experienced/are currently in a period of remission, i.e., the patient did not have refractory disease - Young people whose clinical condition precludes their meaningful involvement in interviews, including those 16 years and older who do not have the capacity to consent will be excluded
Eligibility Criteria: Parents
- Parent or guardian of a child or young person who has had a diagnosis of medulloblastoma or ependymoma. - Their child was treated in the UK or Ireland's paediatric oncology services - Their child is currently or was receiving surveillance imaging following treatment - Their child experienced/are currently in a period of remission, i.e., the patient did not have refractory disease
Eligibility Criteria: All Participants
- Participants who are likely to experience high levels of distress (e.g., Parents who are recently bereaved, if the child/young person is very unwell, or following advice from the clinical team) will be excluded.

Recruitment

CYP with ependymoma or medulloblastoma and their parents will be recruited to this study using two methods:

a) A recruitment advert for the qualitative study will be posted on social media by the research team, and charities (Candlelighters and the Brain Tumour Charity). The post will also be shared by our patient public involvement (PPI) members on closed Facebook groups for parents of CYP with cancer (the research team will not access these groups).Those who are interested will be signposted to the contact details for the researcher (LS), who will send those interested in taking part an information sheet providing details about the study and will follow-up with them after at least 24 hours to check whether they wish to participate in the study.

b) Eligible participants will also be identified following dialogue with the clinical team at one National Health Service (NHS) site (Leeds Children's Hospital). Potentially eligible participants will be approached by members of the clinical team, who will provide interested individuals with a study information pack: including an invitation letter, a participant information sheet, and a consent to contact form. These can be filled in for both the parent and CYP who may wish to take part. Those who complete the consent to contact form will be contacted after at least 24 hours to check whether they wish to participate.

Data Collection

Interviews will be conducted either in person, or on a video call. The participants can choose where (if in-person) and when the interview takes place (i.e., at the weekend or in the evening).

Participants will have the option to use interpreters if their first language is not English, or if they have a speech or hearing impairment. CYP recruited at Leeds Children's Hospital will have the option to use a play-specialist that they know to facilitate their interview.

Before the start of the interview, written or recorded (in a separate video recording) informed consent will be obtained. Following consent, the interview will be audio and video recorded and transcribed as verbatim. Only the audio recording will be used for transcription, and video recordings will be immediately deleted following the interview. See the Supplementary Material for further details.

A toolkit of resources including activities such as toys, photography or an activity book, which have been used in this population previously (25-27) will be used to facilitate conversations about surveillance imaging with CYP. For CYP who do not wish to use these resources, informal semi-structured interviews will be offered. Depending on the preference of the child, parents may be present during the interview, and we anticipate that children aged six or younger will wish to have their parents to stay with them during the interview. The impact of the parent's presence will be assessed during analysis. It is anticipated that interviews will last between 15 and 45 minutes.

Parents will be invited to participate in a semi-structured interview, which is anticipated to last around 45-60 minutes. If both parents of a child wish to take part, they will be offered the opportunity to be interviewed together as a group, or individually.

A topic guide used for the interviews with CYP and parents has been developed deductively based on previous literature (24, 28, 29), before being validated by the study's PPI group. The full topic guide is provided in the Supplementary Material.

Participants will receive a voucher as recognition of them giving time to the research study. CYP will receive a £20 voucher, and adults will receive a £40 voucher. This is consistent for members of the public considering involvement in research as per the National Institute for Health and Care Research INVOLVE guidelines (30).

Analysis

An integrated approach to data analysis, known as 'following the thread' will be used (31, 32). First, analysis will be completed separately for each group of participants (children, young people and parents). Key themes identified in one group will then be explored in the transcripts from the other groups to create a constellation of findings (a 'thread'). This is repeated for other themes identified in the transcripts. Finally, all threads are integrated and analysed as a whole.

Analysis will be conducted by one researcher (LS) using the NVivo software (33). To maintain high quality analysis, preliminary findings from the research will be discussed with the wider research team and the study's PPI group to ensure credibility and authenticity. Member checking, whereby the participants will be able to comment on the results of the study, will also be conducted to ensure the participant's experiences are captured in the results of the study.

Workstream 2

Individual Participant Data

Medulloblastoma Dataset

In collaboration with Newcastle University, we aim to access to the Newcastle Medulloblastoma (NMB) dataset to use in the analysis. This retrospective cohort includes children and young people aged 0-18 with relapsed medulloblastoma who have been treated in the UK (6). This cohort provides a comprehensive dataset of children and young people with relapsed medulloblastoma and includes important information on some of the prognostic factors that may impact outcomes, such as the principal molecular group of medulloblastoma and genetic alterations.

Additional ethical approval is required obtain additional data on method of relapse detection to supplement the NMB dataset, to allow additional data on method of relapse detection to be collected.

IPD from the cohort will be received in a de-identified format, via a secure internet transfer. All data will be transferred in encrypted form, or with password protection. The study coordinator will email the relevant password or decryption key to the researcher separately from the data.

Inclusion and Exclusion Criteria

For Workstream 2 analysis, CYP aged 0-18 with a diagnosis of medulloblastoma (either by MRI imaging or biopsy) who were treated from 2000 in the UK will be included. CYP must have experienced a clinical remission on MRI imaging at the end of treatment, and then have had a confirmed relapse on MRI imaging or biopsy. Further eligibility for the SCAN-ME study will be based on the medulloblastoma cohort's inclusion/exclusion criteria (34).

Core Variables

A variety of variables will be collected, based on availability of data and clinical importance based on experience of a number of paediatric oncologists and the PPI group:

- **Method of relapse detection:** relapse detected on a routinely scheduled MRI scan; relapsed detected by the presence of symptoms, confirmed by MRI scan outside normal scanning routine.
- **Frequency of scans:** details of surveillance imaging protocol and duration between routine appointments.
- Age
- Sex or gender
- **Radiation therapy at diagnosis:** dose, field, location
- Surgical resection at diagnosis
- Prior chemotherapy: drug, dose, frequency, and duration of administration
- **Pattern and location of relapse:** local or distant; disseminated or nodular relapse
- **Molecular subtype (5):** WNT-type; SHH-type; Group 3 and Group 4 medulloblastoma

- **Histological diagnosis:** Classic; large cell anaplastic and desmoplastic/nodular

Data Analysis

Data analysis will be conducted by the lead researcher (LS) with support from the wider research team (BP, AM and KA). A statistical analysis plan (see Supplementary Material) which provides additional details on the analyses, will be reviewed by an external medical statistician (MS) prior to data analysis. All analyses will be conducted in R (36).

The efficacy of surveillance imaging will be measured by evaluating overall survival (OS). The primary outcome measure will be overall survival from diagnosis until death, to avoid the impact of lead time bias. In addition, analysis of OS from relapse will be used as for illustrative purposes to explore the impact of lead-time bias on the association between OS and method of relapse detection.

Survival analysis will be used to assess whether CYP whose relapse was identified by scans in a pre-symptomatic stage have improved overall survival compared to those whose tumour was detected as a result of clinical signs and symptoms. The type of analysis will be determined following clinical advice and will depend on the availability of the data. Hazard ratios will be calculated for each time-to-event outcome.

If sufficient data are available, multivariable analysis will be used to determine whether, detecting a relapse asymptomatically on a scan is more beneficial for some patients, depending on their specific characteristics, compared to others. These characteristics could include whether the child's tumour was subject to gross-total resection (GTR), and tumour-specific predictors (such as molecular subgroup or tumour location). We will look at- where available - whether ethnicity and sex are effect modifiers.

Additional logistic regression analyses will be conducted, to determine whether surveillance imaging is more likely to detect slower growing tumours (as more aggressive tumours are asymptomatic for shorter periods of time). For the logistic regression analyses, the outcome of interest is an asymptomatic relapse **-** whereby a relapse is detected as a part of a routine surveillance imaging protocol. Analyses will be used to explore the association between patient and disease characteristics and the likelihood of a relapse being detected on a scan. Caution will be taken to ensure a sufficient number of participants are being included in each analysis.

Workstream 3

Economic modelling will be used to establish whether surveillance imaging is cost-effective method of detecting a relapse in CYP with medulloblastoma, by using the effectiveness outcomes estimated in Workstream 2, quality adjusted life year (QALY) estimates and associated costs and resource use.

Identifying Relevant Literature

A systematic literature review will be conducted to identify any relevant evidence on the cost-effectiveness of surveillance imaging for CYP with medulloblastoma and relevant studies with data on health-related quality of life, cost and healthcare resource use. A search strategy will be developed with an information specialist, with input from clinical specialists to guide appropriate data cut-offs and search terms. One reviewer will review title and abstracts, and then full texts for inclusion. Studies that meet the inclusion criteria will be summarised in tables.

Model Structure

The final model structure will not be determined until the extent of the available data is known; however, it is anticipated that it will include a number of health states that capture the period of remission following primary treatment, treatable and untreatable relapse, and death. Transition probabilities between these health states will be informed by Workstream 2 analyses. This model will be developed using a life-time horizon, so additional epidemiological evidence to support long-term outcomes for CYP with medulloblastoma will be used. We will discuss potential sources of evidence with clinical experts.

This model will explore whether the addition of surveillance imaging to detect an asymptomatic relapse alongside symptomatic detection, compared to offering no surveillance imaging where relapse can only be detected based on symptoms. Frequency of scans will be obtained from currently open trial protocols for CYP with medulloblastoma, or from clinical expertise.

The following parameters will be sought from the individual participant data from Workstream 2, the systematic literature review, and from clinical advice.

a) **Transition Probabilities:** Clinical effectiveness parameters will be obtained from the individual participant data analysis from Workstream 2. This will include overall survival, progression-free survival (following first, and later lines of therapy), and incidence of disease relapse.
b) **Quality of Life:** Each health state will be associated with a quality of life which will be obtained from the systematic literature review.
c) **Resource Use and Unit Costs:** Costs associated with conducting surveillance imaging, and other clinical appointments, as well as costs linked to management of relapse, and supportive care will be identified. Resource utilisation will be obtained from published data and advice from clinical experts. Costs will be obtained from resources such as Personal Social Services Research Unit (PSSRU) and NHS reference costs.
d) **Time Horizon and Discounting of Future Outcomes:** In accordance with the National Institute of Health and Care Excellence (NICE) reference case, the analysis will adopt a lifetime horizon. Future QALYs and costs will be discounted at an annual rate of 3.5% (37). A scenario analysis using a societal perspective, to account for the additional costs and impact on quality of life associated with surveillance imaging for CYP and their parents will be conducted.

Modelling Uncertainty

A probabilistic sensitivity analysis (PSA) will be performed to reflect the fact that the model parameters are estimated with uncertainty, and in the case of the transition probabilities are likely to be obtained from small sample sizes. From this, it is possible to evaluate the impact that this uncertainty may have on the conclusions of the cost-effectiveness analysis. This is achieved by estimating the probability that surveillance imaging is cost-effective as a function of different cost-effectiveness threshold levels and plotting this information in a cost-effectiveness acceptability curve (38).

Subgroup Analysis

Owing to heterogeneity in the tumour characteristics and prognosis, medulloblastoma and ependymoma will be modelled separately, and separate ICERs will be presented. Depending on the availability of the data, further subgroups, such as whether patients receive radiotherapy as a first-line therapy or whether radiotherapy-sparing treatments were used may be considered. Any decisions to conduct subgroup analyses will be made following clinical advice.

Value of Information Analysis

Uncertainty in results will be characterised and explored in the economic evaluation through a value of information analysis, which quantifies the monetary value in conducting additional research to reduce uncertainties within the research question (39).

The output from the PSA will be used to conduct a value of information analysis to quantify the value of conducting further research compared to the costs of additional investigation Using the output from the PSA, the value of information analysis will estimate the value of perfect information (EVPI) - the cost at which all uncertainties in the current analysis (including the clinical-effectiveness of surveillance imaging and the associated quality of life benefits) are removed, and the expected value of partially perfect information (EVPPI)- the cost at which some of the uncertainties within the current analysis are addressed. If there is sufficient data, the EVPI and EVPPI will be conducted for particular subgroups to determine whether there is a greater need for further research in particular groups of CYP (based on particular prognostic characteristics) compared to others.

Combining Results from the Workstreams

Once data analysis has been conducted separately in each workstream, the findings will be combined, and analysis will focus on the extent to which the findings regarding the value of surveillance imaging from the three elements of the PhD converge or diverge (40). First, the key findings from each workstream relating to the **value** of surveillance imaging will be collated before comparing the results by assessing how valuable scans were in terms of clinical effectiveness, their value for money, and their importance and meaning to families of CYP with ependymoma and medulloblastoma. The combined results will be presented side-by-side in a summary table and explored further in a discussion.

As this study will combine data from distinct samples (participants the clinical trials and participants recruited for the qualitative work), differences between the patient demographics

will be explored and the discussion will include a description on how this may have affected the results.

Discussion

Families with experience of surveillance imaging who we have worked with when developing this project described a sawtooth of emotions during the period of surveillance imaging following treatment (described in the literature as 'scanxiety' (41, 42)) and talked about their dependence on surveillance imaging to reassure them that the tumour had not recurred. The PPI group considered it important to determine whether surveillance imaging improved outcomes for CYP with medulloblastoma and ependymoma, but also to explore the experiences of those who have undergone surveillances as they considered that these may vary substantially.

This paper describes a protocol for the SCAN-ME study: a mixed-methods study evaluating the value of surveillance imaging for CYP with medulloblastoma and ependymoma. The study has the potential to impact families, clinicians, and decision makers by providing a holistic picture about the value of surveillance imaging within this population.

The qualitative workstream of this the SCAN-ME study will explore family's experiences of surveillance imaging following treatment for medulloblastoma and ependymoma. This will provide important insight into their perspective of scans and have the potential to impact future care and support for CYP and their parents in the period of follow-up care after treatment ends.

The efficacy of surveillance imaging for ependymoma and medulloblastoma remains uncertain, especially in the cases where prognosis after relapse is poor (14, 16). Difficulties in accurately measuring survival, owing to the impact of lead-time bias have made it more uncertain. The SCAN-ME study will utilise individual participant data to evaluate the effectiveness of surveillance imaging accurately by minimising the impact of lead-time bias. Not only this but the study will also evaluate the issue of length time bias by controlling for potential confounding variables. This will provide more clarity to decision makers as to whether surveillance imaging is effective for medulloblastoma, or whether it should only be utilised in particular subgroups.

Not only do decision makers need to consider the clinical effectiveness of surveillance imaging, but also whether surveillance imaging is value for money for healthcare reimbursement agencies. This will be addressed by comparing whether the additional costs associated with providing surveillance imaging is value for money compared to any improvements in clinical benefits and health-related quality of life. To our knowledge, this is the first economic analysis of surveillance imaging in this population.

The findings from the study will be discussed with stakeholders including clinicians and our PPI group, to ensure that the conclusions and implications to clinical practice are relevant. This is likely to be especially important in a situation where the results of the workstreams conflict – for example, if scans are found to not improve survival outcomes and is cost-ineffective but are deemed an important aspect of follow-up care to families of a child with medulloblastoma or ependymoma.

List of Abbreviations

CYP, children and young people; CNS, central nervous system; PPI, patient public involvement; NHS, National Health Service; PSA, probabilistic sensitivity analysis; EVPI, estimating the value of perfect information; EVPPI, expected value of partially perfect information.

Declarations

Ethics approval and consent to participate

This study has received ethical approval from the West Midlands – Coventry and Warwickshire Research Ethics Committee on 05/09/2023 (reference: 23/WM/0176). The study will be conducted to protect the human rights and dignity of the participants as reflected in the 1996 version of the Helsinki Declaration.

Informed consent to participate in the study will be obtained for all participants over the age of 16. Children who are under the age of 16 will be able to provide consent if they can comprehend the study's objectives and the consequences of their decision to take part (43). For those who do not have the competence or maturity to consent, the study will use a two-stage consent/assent process. Further details are provided in the Supplementary Material.

Consent for publication

Not applicable

Availability of data and materials

Not applicable

Competing interests

The authors have no competing interests to declare

Funding

This study/project is funded by the NIHR (NIHR302612). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Authors' contributions

LS and BP contributed to the conception or design of the work; KA and AM have contributed to the methods outlined in the protocol; LS drafted protocol; BP, KA and AM have revised the protocol, and have approved the submitted version. LS, BP, KA and AM have agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

Acknowledgements

The authors would like to acknowledge Dr Mark Simmonds who will be providing external review of the statistical analysis planned in this protocol.

References

1. Children's Cancer and Leukaemia Group. Brain tumours 2022 [Available from: https://www.cclg.org.uk/brain-tumours.
2. Cancer Research UK. Children's cancers mortality statistics 2021 [Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/childrens-cancers/mortality#heading-Three.
3. Children with Cancer UK. Spinal and brain tumours in children 2019 [Available from: https://www.childrenwithcancer.org.uk/childhood-cancer-info/cancer-types/brain-spinal-tumours/.
4. National Cancer Registration and Analysis Service. Appendix B CTYA UK cancer incidence and survival tabulations 2021 [Available from: http://www.ncin.org.uk/cancer_type_and_topic_specific_work/cancer_type_specific_work/cancer_in_children_teenagers_and_young_adults/.
5. Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, et al. The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathologica. 2016;131(6):803-20.
6. Hill RM, Richardson S, Schwalbe EC, Hicks D, Lindsey JC, Crosier S, et al. Time, pattern, and outcome of medulloblastoma relapse and their association with tumour biology at diagnosis and therapy: a multicentre cohort study. Lancet Child Adolesc Health. 2020;4(12):865-74.
7. Sowar K, Straessle J, Donson AM, Handler M, Foreman NK. Predicting which children are at risk for ependymoma relapse. J Neurooncol. 2006;78(1):41-6.
8. Hill RM, Plasschaert SL, Timmermann B, Dufour C, Aquilina K, Avula S, et al. Relapsed medulloblastoma in pre-irradiated patients: current practice for diagnostics and treatment. Cancers. 2021;14(1):126.
9. Byer L, Kline CN, Coleman C, Allen IE, Whitaker E, Mueller S. A systematic review and meta-analysis of outcomes in pediatric, recurrent ependymoma. Journal of Neuro-Oncology. 2019;144(3):445-52.
10. Malhotra AK, Nobre LF, Ibrahim GM, Kulkarni AV, Drake JM, Rutka JT, et al. Outcomes following management of relapsed pediatric posterior fossa ependymoma in the molecular era. Journal of Neuro-Oncology. 2023;161(3):573-82.
11. Klawinski D, Indelicato DJ, Hossain J, Sandler E. Surveillance imaging in pediatric ependymoma. Pediatr Blood Cancer. 2020;67(11):e28622.
12. Main C, Stevens SP, Bailey S, Phillips R, Pizer B, Wheatley K, et al. The impact of routine surveillance screening with magnetic resonance imaging (MRI) to detect tumour recurrence in children with central nervous system (CNS) tumours: protocol for a systematic review and meta-analysis. Syst Rev. 2016;5(1):143.
13. Yalçin B, Büyükpamukçu M, Akalan N, Cila A, Kutluk MT, Akyüz C. Value of surveillance imaging in the management of medulloblastoma. Med Pediatr Oncol. 2002;38(2):91-7.
14. Bouffet E, Doz F, Demaille MC, Tron P, Roche H, Plantaz D, et al. Improving survival in recurrent medulloblastoma: earlier detection, better treatment or still an impasse? Br J Cancer. 1998;77(8):1321-6.

15. Good CD, Wade AM, Hayward RD, Phipps KP, Michalski AJ, Harkness WFJ, et al. Surveillance neuroimaging in childhood intracranial ependymoma: how effective, how often, and for how long? Journal of Neurosurgery. 2001;94(1):27-32.
16. Torres CF, Rebsamen S, Silber JH, Sutton LN, Bilaniuk LT, Zimmerman RA, et al. Surveillance scanning of children with medulloblastoma. N Engl J Med. 1994;330(13):892-5.
17. Elit L, Pond GR, Levine MN. Routine imaging or no routine imaging, is that the question? Journal of the National Comprehensive Cancer Network. 2020;18(4):490-2.
18. Sabel M, Fleischhack G, Tippelt S, Gustafsson G, Doz F, Kortmann R, et al. Relapse patterns and outcome after relapse in standard risk medulloblastoma: a report from the HIT-SIOP-PNET4 study. J Neurooncol. 2016;129(3):515-24.
19. Massimino M, Barretta F, Modena P, Giangaspero F, Chiapparini L, Erbetta A, et al. Pediatric intracranial ependymoma: correlating signs and symptoms at recurrence with outcome in the second prospective AIEOP protocol follow-up. Journal of Neuro-Oncology. 2018;140(2):457-65.
20. Kay BR, Witte D. The impact of cancer biology, lead time bias, and length bias in the debate about cancer screening tests. J Insur Med. 1991;23(2):102-4.
21. Kovanlikaya A, Karabay N, Cakmakçi H, Uysal K, Olgun N, Ergör G. Surveillance imaging and cost effectivity in pediatric brain tumors. Eur J Radiol. 2003;47(3):188-92.
22. Young K, Bowers A, Bradford N. Families' experiences of child and adolescent brain tumor: A systematic review and synthesis of qualitative research. Psychooncology. 2021;30(10):1643-62.
23. Stevens SP, Main C, Bailey S, Pizer B, English M, Phillips R, et al. The utility of routine surveillance screening with magnetic resonance imaging (MRI) to detect tumour recurrence in children with low-grade central nervous system (CNS) tumours: a systematic review. Journal of Neuro-oncology. 2018;139:507-22.
24. Tyldesley-Marshall N, Greenfield S, Neilson S, English M, Adamski J, Peet A. Qualitative study: patients' and parents' views on brain tumour MRIs. Arch Dis Child. 2020;105(2):166-72.
25. Breitwieser CL, Vaughn LM. “A Day in My life” Photography Project:The Silent Voice of Pediatric Bone Marrow Transplant Patients. Journal of Pediatric Oncology Nursing. 2014;31(5):284-92.
26. Bryan G, Bluebond-Langner M, Kelly D, Kumpunen S, Oulton K, Gibson F. Studying Children’s Experiences in Interactions With Clinicians: Identifying Methods Fit for Purpose. Qualitative Health Research. 2019;29(3):393-403.
27. Gibson F, Aldiss S, Horstman M, Kumpunen S, Richardson A. Children and young people's experiences of cancer care: a qualitative research study using participatory methods. Int J Nurs Stud. 2010;47(11):1397-407.
28. Shuldiner J, Shah N, Corrado AM, Hodgson D, Nathan PC, Ivers N. Determinants of surveillance for late effects in childhood cancer survivors: a qualitative study using the Theoretical Domains Framework. J Cancer Surviv. 2022;16(3):552-67.
29. Tutelman PR, Heathcote LC. Fear of cancer recurrence in childhood cancer survivors: A developmental perspective from infancy to young adulthood. Psycho-Oncology. 2020;29(11):1959-67.
30. National Institute for Health and Care Research. Payment guidance for researchers and professionals, Version 1.3 2022 [Available from: https://www.nihr.ac.uk/documents/payment-guidance-for-researchers-and-professionals/27392.

31. Cronin A, Alexander V, Fielding J, Moran-Ellis J, Thomas H. The analytic integration of qualitative data sources. The SAGE handbook of social research methods. 2008.
32. Moran-Ellis J, Alexander VD, Cronin A, Dickinson M, Fielding J, Sleney J, et al. Triangulation and integration: processes, claims and implications. Qualitative research. 2006;6(1):45-59.
33. QSR International Pty Ltd. NVivo (released in March 2020) 2020 [Available from: https://www.qsrinternational.com/nvivo-qualitative-data-analysis-software/home.
34. Hill RM, Plasschaert SLA, Timmermann B, Dufour C, Aquilina K, Avula S, et al. Relapsed Medulloblastoma in Pre-Irradiated Patients: Current Practice for Diagnostics and Treatment. Cancers (Basel). 2021;14(1).
35. Leblond P, Massimino M, English M, Ritzmann TA, Gandola L, Calaminus G, et al. Toward Improved Diagnosis Accuracy and Treatment of Children, Adolescents, and Young Adults With Ependymoma: The International SIOP Ependymoma II Protocol. Front Neurol. 2022;13:887544.
36. R Development Core Team. R: A language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2008.
37. National Institute for H, Care E. NICE Process and Methods Guides. Guide to the Methods of Technology Appraisal 2013. London: National Institute for Health and Care Excellence (NICE)
Copyright © 2013 National Institute for Health and Clinical Excellence, unless otherwise stated. All rights reserved.; 2013.
38. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. Health Economics. 2001;10(8):779-87.
39. Claxton KP, Sculpher MJ. Using value of information analysis to prioritise health research: some lessons from recent UK experience. Pharmacoeconomics. 2006;24(11):1055-68.
40. Creswell J, Plano Clark V. Designing and conducting mixed methods research. 2 ed. Los Angeles, London: SAGE; 211.
41. Heathcote LC, Cunningham SJ, Webster SN, Tanna V, Mattke E, Loecher N, et al. Smartphone-based Ecological Momentary Assessment to study "scanxiety" among Adolescent and Young Adult survivors of childhood cancer: A feasibility study. Psycho-Oncology. 2022;31(8):1322-30.
42. Kim Tam B, Roger L, Belinda EK, Chris B, Haryana MD, Prunella B. Scanxiety: a scoping review about scan-associated anxiety. BMJ Open. 2021;11(5):e043215.
43. Phillips B, Davies HT, Preston J, Stones SR. Framework to help design and review research involving children. Arch Dis Child. 2019;104(6):601-4.

Protocol including Track Changes

Background

Brain and central nervous system (CNS) tumours are the second commonest cancer in children and young people (CYP), affecting around 400 individuals in Great Britain every year (1). Although survival outcomes for CYP with brain and CNS tumours has improved significantly over the past few decades, there is still variation in outcomes across tumour types, meaning they account for a disproportionate number of deaths in CYP with cancer (2, 3).

Medulloblastoma is the most common malignant brain tumour in CYP, affecting around 58 CYP in the UK every year (4). Medulloblastoma includes four different subgroups, which vary in their clinical and genetic features and in their prognosis (5, 6). Ependymomas are another type of malignant brain tumours which affect around 37 CYP in the UK every year (4). Although a greater proportion of patients with ependymoma will experience a relapse ~~([~~around 50% (7)~~),],~~ compared to medulloblastoma ~~([~~around 30% (6)~~), outcomes following survival are better for ependymoma, with 25% patients surviving subsequent treatment and relapses, especially for those who achieve gross total resection from surgery. Prognosis~~] the prognosis for relapsed medulloblastoma is much worse, with less than 5% surviving, and treatments following relapse are typically non-curative (8). Patterns of relapse in ependymoma are more heterogenous: children and young people with ependymoma may experience a relatively short survival period following relapse, others experience chronically relapsing disease (9, 10).

A brain ~~and /~~CNS tumour relapse can be detected in two ways: either by the presence of symptoms, or asymptomatically- where a tumour is detected on an MRI scan that was administered as part of a regular ~~follow-up~~ schedule of ~~check~~follow-up appointments. Surveillance imaging aims to detect a recurrence before clinical symptoms develop, with the ~~intention to improve the survival outcomes, increase the treatment options available, or minimise the complications from treatment~~ presumption that earlier detection of relapse will lead to improved outcomes (11-13).

The utility of surveillance imaging in medulloblastoma and ependymoma has long been debated (11, 14-16)~~, especially as issues~~. Issues of lead-time bias (which produces a perceived improved survival when using surveillance imaging, as tumour recurrences are detected earlier) often impact the validity of the results (17). This is evidenced in study which found that although CYP with medulloblastoma whose relapse was detected symptomatically had shorter survival if measured from the point of relapse compared to those detected using MRI, overall survival when measured from primary diagnosis did not differ (18)~~.~~. Many studies exploring the utility of surveillance imaging in ependymoma that find significant improvement in outcomes measure survival from relapse. Given the potential impact of lead-time bias means there is uncertainty in the utility of surveillance imaging in this population (15, 19). Where survival is measured from the same point in the disease trajectory, survival – while longer in the surveillance group – was not significantly different to those whose relapse was detected by symptoms (11). Furthermore, length bias may be an issue, where the tumours detected by scans are prognostically different (slower growing in more favourable places, more amenable to be treated with local therapies) to those detected by symptoms (faster growing, disseminated, harder to treat with local therapies), meaning the efficacy of surveillance imaging can be confounded by other prognostic variables ~~(10, 12, 16)~~(11, 14, 20). Finally, in the case of medulloblastoma, some argue that surveillance imaging is currently futile, as an early detection of a relapse will unlikely change outcomes given the lack of curative options at second-line (14, 16).

~~There~~The provision of surveillance imaging also has cost implications on health care services and resources. Despite this, there are no studies evaluating the cost-effectiveness of surveillance imaging in CYP with medulloblastoma or ependymoma. One cost-minimisation analysis study suggested that there were no significant differences between the cost of surveillance imaging for all paediatric brain tumours and standard follow-up care~~, however~~. However the limited description of the methods used, and lack of consideration of quality of life or any other measurement of health benefit, mean the results are unlikely to be representative or applicable in the UK health sector and cannot inform decision makers regarding the value for money of surveillance imaging (21).

Notwithstanding, the biggest source of uncertainty-related anxiety for families was the fear of cancer recurrence ~~(18). While surveillance imaging can reassure CYP and their families that the tumour has not recurred, it has a considerable impact on families' quality of life (19). One qualitative study found that while having scans can reassure~~

~~families, and improve their sense of control, waiting for results can be a difficult and anxious time~~ (22). While surveillance imaging can reassure CYP and their families that the tumour has not recurred, it has a considerable impact on families' quality of life (23). One qualitative study found that while having scans can reassure families, and improve their sense of control, waiting for results can be a difficult and anxious time (24).

Therefore, in order for earlier asymptomatic detection of relapse to be valuable and worthwhile, it is important to weigh up the broader benefits, risks, and costs of early detection.

Methods

The SCAN-ME study has three workstreams. Each workstream of this study aims to assess the **value** of surveillance imaging for CYP with medulloblastoma and ependymoma. The objectives are:

- **Workstream 1:** To understand CYP with medulloblastoma and ependymoma and their parents' experiences and expectations of surveillance imaging.
- **Workstream 2:** To determine whether identifying an asymptomatic medulloblastoma and ependymoma relapse in CYP using surveillance imaging is clinically effective and improves overall and event-free survival following relapse.
- **Workstream 3:** To establish the cost-effectiveness of surveillance imaging compared to the use of symptomatic detection alone in CYP with medulloblastoma and ependymoma.

Workstream 1

Workstream 1 is a qualitative study which will explore the experiences and expectations of surveillance imaging for CYP with medulloblastoma and ependymoma and their parents.

Participants

CYP with medulloblastoma or ependymoma who have finished treatment, and their parents will be invited to participate in this study (see Table 1 for the eligibility criteria). To ensure the sample is reflective of families with experience of medulloblastoma or ependymoma, we will actively seek to recruit participants with a range of different familial and tumour-specific characteristics (e.g., ethnicity, socioeconomic status, age of child, tumour subgroup, requirement of general anaesthetic for the scans, and experience of tumour relapse).

Table 1. Eligibility Criteria for Workstream 1

Eligibility Criteria: Children and Young People
- Child or young person must with a diagnosis of medulloblastoma or ependymoma - ~~Treated in Leeds Children's Hospital~~ - Are currently receiving surveillance imaging following treatment - Experienced/are currently in a period of remission, i.e., the patient did not have refractory disease - Young people whose clinical condition precludes their meaningful involvement in interviews, including those 16 years and older who do not have the capacity to consent will be excluded
Eligibility Criteria: Parents
- Parent or guardian of a child or young person who has had a diagnosis of medulloblastoma or ependymoma. - Their child was treated in the UK or Ireland's paediatric oncology services - Their child is currently or was receiving surveillance imaging following treatment - Their child experienced/are currently in a period of remission, i.e., the patient did not have refractory disease
Eligibility Criteria: All Participants
- Participants who are likely to experience high levels of distress (e.g., Parents who are recently bereaved, if the child/young person is very unwell, or following advice from the clinical team) will be excluded.

Recruitment

CYP with ependymoma or medulloblastoma and their parents will be recruited to this study using two methods:

c) A recruitment advert for the qualitative study will be posted on social media by the research team, and charities (Candlelighters and the Brain Tumour Charity). The post will also be shared by our patient public involvement (PPI) members on closed Facebook groups for parents of CYP with cancer (the research team will not access these groups). ~~PPI members will signpost those~~Those who are interested will be signposted to the contact details for the researcher (LS), who will send those interested in taking part an information sheet providing details about the study and will follow-up with them after at least 24 hours to check whether they wish to participate in the study.

d) Eligible participants will also be identified following dialogue with the clinical team at one National Health Service (NHS) site (Leeds Children's Hospital). Potentially eligible participants will be approached by members of the clinical team, who will provide interested individuals with a study information pack: including an invitation letter, a participant information sheet, and a consent to contact form. These can be filled in for both the parent and CYP who may wish to take part. Those who complete the consent to contact form will be contacted after at least 24 hours to check whether they wish to participate.

Data Collection

Interviews will be conducted either in person, or on a video call. The participants can choose where (if in-person) and when the interview takes place (i.e., at the weekend or in the evening). Participants will have the option to use interpreters if their first language is not English, or if they have a speech or hearing impairment. CYP recruited at Leeds Children's Hospital will have the option to use a play-specialist that they know to facilitate their interview.

Before the start of the interview, written or recorded (in a separate video recording) informed consent will be obtained. Following consent, the interview will be audio and video recorded and transcribed as verbatim. Only the audio recording will be used for transcription, and video recordings will be immediately deleted following the interview. See the Supplementary Material for further details.

A toolkit of resources including activities such as toys, photography or an activity book, which have been used in this population previously (25-27) will be used to facilitate conversations about surveillance imaging with CYP. For CYP who do not wish to use these resources, informal semi-structured interviews will be offered. Depending on the preference of the child, parents may be present during the interview, and we anticipate that children aged six or younger will wish to have their parents to stay with them during the interview. The impact of the parent's presence will be assessed during analysis. It is anticipated that interviews will last between 15 and 45 minutes.

Parents will be invited to participate in a semi-structured interview, which is anticipated to last around 45-60 minutes. If both parents of a child wish to take part, they will be offered the opportunity to be interviewed together as a group, or individually.

A topic guide used for the interviews with CYP and parents has been developed deductively based on previous literature (24, 28, 29), before being validated by the study's PPI group. The full topic guide is provided in the Supplementary Material.

Participants will receive a voucher as recognition of them giving time to the research study. CYP will receive a £20 voucher, and adults will receive a £40 voucher. This is consistent for members of the public considering involvement in research as per the National Institute for Health and Care Research INVOLVE guidelines (30).

Analysis

An integrated approach to data analysis, known as 'following the thread' will be used (31, 32). First, analysis will be completed separately for each group of participants (children, young people and parents). Key themes identified in one group will then be explored in the transcripts from the other groups to create a constellation of findings (a

'thread'). This is repeated for other themes identified in the transcripts. Finally, all threads are integrated and analysed as a whole.

Analysis will be conducted by one researcher (LS) using the NVivo software (33). To maintain high quality analysis, preliminary findings from the research will be discussed with the wider research team and the study's PPI group to ensure credibility and authenticity. Member checking, whereby the participants will be able to comment on the results of the study, will also be conducted to ensure the participant's experiences are captured in the results of the study.

Workstream 2

~~Individual participant data from to two UK studies will be requested, to evaluate the clinical and cost-effectiveness of surveillance imaging.~~

Individual Participant Data

Medulloblastoma Dataset

In collaboration with Newcastle University, we aim to access to the Newcastle Medulloblastoma (NMB) dataset to use in the analysis. This retrospective cohort includes children and young people aged 0-18 with relapsed medulloblastoma who have been treated in the UK (6). This cohort provides a comprehensive dataset of children and young people with relapsed medulloblastoma and includes important information on some of the prognostic factors that may impact outcomes, such as the principal molecular group of medulloblastoma and genetic alterations.

Additional ethical approval is required obtain additional data on method of relapse detection to supplement the NMB dataset, to allow additional data on method of relapse detection to be collected.

~~*Ependymoma Dataset*~~

~~In collaboration with Nottingham University, we have been granted access to the Ependymoma Multi-Disciplinary Advisory Group (EMAG) dataset. This dataset has collected data on patients who were treated as part of the SIOP II Ependymoma (SIOP EPII) trial from 2015 to present who were treated in the UK. The cohort includes children and young people up to the age of 22 with newly diagnosed ependymoma. For the SCAN-ME study, we will only use data on children and young people who experienced a relapse, this included 68 patients.~~

~~Data on the method of relapse detection was not collected in the EMAG dataset. To obtain this information, the EMAG forms of the relapsed patients will be reviewed by EMAG dataset collaborators, and method of relapse detection inferred based on clinical notes surrounding reasoning for requesting scans (e.g., requesting as a routine follow-up, or requesting following indication of clinical symptoms).~~

IPD from the cohort~~s~~ will be received in a de-identified format, via a secure internet transfer. All data will be transferred in encrypted form, or with password protection. The study coordinator will email the relevant password or decryption key to the researcher separately from the data.

Inclusion and Exclusion Criteria

For Workstream 2 analysis, CYP aged 0-18 with a diagnosis of medulloblastoma ~~or ependymoma~~ (either by MRI imaging or biopsy) who were treated from 2000 in the UK will be included. CYP must have experienced a clinical remission on MRI imaging at the end of treatment, and then have had a confirmed relapse on MRI imaging or biopsy. Further eligibility for the SCAN-ME study will be based on the medulloblastoma~~/ependymoma~~ cohort's inclusion/exclusion criteria (34~~, 35~~).

Core Variables

A variety of variables will be collected, including but not limited to those described in Table 2, based on availability of data and clinical importance based on experience of a number of paediatric oncologists and the PPI group (see Table 2).

Table 2. Variables to be obtained from individual participant data.

Generic Variables
- **Method of relapse detection:** relapse detected on a routinely scheduled MRI scan; relapsed detected by the presence of symptoms, confirmed by MRI scan outside normal scanning routine. - **Frequency of scans:** details of surveillance imaging protocol and duration between routine appointments. - Age - Sex or gender - **Radiation therapy at diagnosis:** dose, field, location - Surgical resection at diagnosis - Prior chemotherapy: drug, dose, frequency, and duration of administration - **Pattern and location of relapse:** local or distant; disseminated or nodular relapse
Medulloblastoma-Specific Variables
- **Molecular subtype (5):** WNT-type; SHH-type; Group 3 and Group 4 medulloblastoma - **Histological diagnosis:** Classic; large cell anaplastic and desmoplastic/nodular - **Extent of surgical resection at diagnosis:** gross total resection (GTR); near total resection (<1·5cm^2); subtotal resection (≥ 1·5cm^2)
~~**Ependymoma-Specific Variables**~~
~~**Molecular diagnosis:** as per WHO 2021 classification~~ ~~- **Extent of surgical resection at diagnosis (as per SIOP-EPII protocol (35)):** R0 (no residual tumour on postoperative MRI); R1 (no residual tumour on MRI but description of a small residual tumour by the neurosurgeon); R2 (small residual tumour on MRI with the max diameter <5mm); R3 (residual tumour that can be measured in 3 planes); R4 (size of the residual tumour not differing from the preoperative status); RX (if imaging is inadequate, the term "unclear" should be possible)~~ ~~- **Location at diagnosis:** supratentorial, posterior fossa, spine~~

Data Analysis

Data analysis will be conducted by the lead researcher (LS) with support from the wider research team (BP, AM and KA). A statistical analysis plan (see Supplementary Material) which ~~will be developed when~~ provides additional details on ~~the extent of available data is known~~analyses, will be reviewed by an external medical statistician (MS) prior to data analysis. All analyses will be conducted ~~using~~in R (36).

The efficacy of surveillance imaging will be measured ~~using outcomes~~ by evaluating overall survival (OS) ~~and event-free~~. The primary outcome measure will be overall survival ~~(EFS. OS and EFS will be measured~~from ~~the end of initial treatment~~diagnosis until death, ~~relapse, or the end of study~~ to avoid the impact of lead time bias. In addition, analysis of OS from relapse will be used as for illustrative purposes to explore the impact of lead-time bias on the association between OS and method of relapse detection.

Survival analysis will be used to assess whether CYP whose relapse was identified by scans in a pre-symptomatic stage have improved ~~event-free survival and~~ overall survival compared to those whose tumour was detected as a result of clinical signs and symptoms. The type of analysis will be determined following clinical advice and will depend on the availability of the data. Hazard ratios will be calculated for each time-to-event outcome.

If sufficient data are available, multivariable analysis will be used to determine whether, detecting a relapse asymptomatically on a scan is more beneficial for some patients, depending on their specific characteristics, compared to others. These characteristics could include whether the child's tumour was subject to gross-total resection (GTR), and tumour-specific predictors (such as molecular subgroup or tumour location). We will look at-where available - whether ethnicity and sex are effect modifiers.

~~Previous research has suggested the improved survival outcomes associated with asymptomatic detection may be related to subsequent therapies that they may receive - in this case, whether surgical re-resection or radiotherapy can be provided. This may be due to differences in the type of cancers more commonly detected on a scan (slower~~

~~growing, more nodular disease) which are therefore more amenable to local therapies following relapse, and those detected by the presence of symptoms. Multi-variable survival analyses will be conducted to determine whether survival outcomes are improved when a tumour is detected asymptomatically, after controlling for factors such as nodular disease, local relapse, and use of subsequent local therapies.~~

Additional logistic regression analyses will be conducted, to determine whether surveillance imaging is more likely to detect slower growing tumours (as more aggressive tumours are asymptomatic for shorter periods of time). For the logistic regression analyses, the outcome of interest is an asymptomatic relapse - whereby a relapse is detected as a part of a routine surveillance imaging protocol. Analyses will be used to explore the association between patient and disease characteristics and the likelihood of a relapse being detected on a scan. Caution will be taken to ensure a sufficient number of participants are being included in each analysis.

Workstream 3

Economic modelling will be used to establish whether surveillance imaging is cost-effective method of detecting a relapse in CYP with medulloblastoma ~~and ependymoma~~, by using the effectiveness outcomes estimated in Workstream 2, quality adjusted life year (QALY) estimates and associated costs and resource use.

Identifying Relevant Literature

A systematic literature review will be conducted to identify any relevant evidence on the cost-effectiveness of surveillance imaging for CYP with medulloblastoma and ~~ependymoma and~~ relevant studies with data on health-related quality of life, cost and healthcare resource use. A search strategy will be developed with an information specialist, with input from clinical specialists to guide appropriate data cut-offs and search terms. ~~Two reviewers~~One reviewer will review title and abstracts, and then full texts for inclusion~~, with discrepancies resolved by discussion~~. Studies that meet the inclusion criteria will be summarised in tables.

Model Structure

The final model structure will not be determined until the extent of the available data is known; however, it is anticipated that it will include a number of health states that capture the period of remission following primary treatment, treatable and untreatable relapse, and death. Transition probabilities between these health states will be informed by Workstream 2 analyses. This model will be developed using a life-time horizon, so additional epidemiological evidence to support long-term outcomes for CYP with ~~ependymoma and~~ medulloblastoma will be used. We will discuss potential sources of evidence with clinical experts.

This model will explore whether the addition of surveillance imaging to detect an asymptomatic relapse alongside symptomatic detection, compared to offering no surveillance imaging where relapse can only be detected based on symptoms. Frequency of scans will be obtained from currently open trial protocols for CYP with medulloblastoma ~~or ependymoma~~, or from clinical expertise.

The following parameters will be sought from the individual participant data from Workstream 2, the systematic literature review, and from clinical advice.

e) ~~**Clinical Effectiveness**~~**Transition Probabilities:** Clinical effectiveness parameters will be obtained from the individual participant data analysis from Workstream 2. This will include overall survival, progression-free survival (following first, and later lines of therapy), and incidence of disease relapse.
f) **Quality of Life:** Each health state will be associated with a quality of life which will be obtained from the systematic literature review.
g) **Resource Use and Unit Costs:** Costs associated with conducting surveillance imaging, and other clinical appointments, as well as costs linked to management of relapse, and supportive care will be identified. Resource utilisation will be obtained from published data and advice from clinical experts. Costs will be obtained from resources such as Personal Social Services Research Unit (PSSRU) and NHS reference costs.

h) **Time Horizon and Discounting of Future Outcomes:** In accordance with the National Institute of Health and Care Excellence (NICE) reference case, the analysis will adopt a lifetime horizon. ~~Future QALYs and costs will be discounted at an annual rate of 3.5% (35).~~Future QALYs and costs will be discounted at an annual rate of 3.5% (37). A scenario analysis using a societal perspective, to account for the additional costs and impact on quality of life associated with surveillance imaging for CYP and their parents will be conducted.

Modelling Uncertainty

A probabilistic sensitivity analysis (PSA) will be performed to reflect the fact that the model parameters are estimated with uncertainty~~.~~, and in the case of the transition probabilities are likely to be obtained from small sample sizes. From this, it is possible to evaluate the impact that this uncertainty may have on the conclusions of the cost-effectiveness analysis. This is achieved by estimating the probability that surveillance imaging is cost-effective as a function of different cost-effectiveness threshold levels and plotting this information in a cost-effectiveness acceptability curve (~~36~~38).

Subgroup Analysis

Owing to heterogeneity in the tumour characteristics and prognosis, medulloblastoma and ependymoma will be modelled separately, and separate ICERs will be presented. Depending on the availability of the data, further subgroups, such as whether patients receive radiotherapy as a first-line therapy or whether radiotherapy-sparing treatments were used may be considered. Any decisions to conduct subgroup analyses will be made following clinical advice.

Value of Information Analysis

Uncertainty in results will be characterised and explored in the economic evaluation through a value of information analysis, which quantifies the monetary value in conducting additional research to reduce uncertainties within the research question (39).

The output from the PSA will be used to conduct a value of information analysis to quantify the value of conducting further research compared to the costs of additional investigation ~~(37). This will include estimating~~Using the output from the PSA, the value of information analysis will estimate the value of perfect information (EVPI) - the cost at which all uncertainties in the current analysis (including the clinical-effectiveness of surveillance imaging and the associated quality of life benefits) are removed, and the expected value of partially perfect information (EVPPI)- the cost at which some of the uncertainties within the current analysis are addressed. If there is sufficient data, the EVPI and EVPPI will be conducted for particular subgroups to determine whether there is a greater need for further research in particular groups of CYP (based on particular prognostic characteristics) compared to others.

Combining Results from the Workstreams

Once data analysis has been conducted separately in each workstream, the findings will be combined, and analysis will focus on the extent to which the findings regarding the value of surveillance imaging from the three elements of the PhD converge or diverge ~~(38).~~(40). First, the key findings from each workstream relating to the **value** of surveillance imaging will be collated before comparing the results by assessing how valuable scans were in terms of clinical effectiveness, their value for money, and their importance and meaning to families of CYP with ependymoma and medulloblastoma. The combined results will be presented side-by-side in a summary table and explored further in a discussion.

As this study will combine data from distinct samples (participants the clinical trials and participants recruited for the qualitative work), differences between the patient demographics will be explored and the discussion will include a description on how this may have affected the results. ~~The findings from the study will be discussed with paediatric oncologists and our PPI group, to ensure that the conclusions and implications to clinical practice are realistic.~~

Discussion

Families with experience of surveillance imaging who we have worked with when developing this project described a sawtooth of emotions during the period of surveillance imaging following treatment (described in the literature as

'~~Scanxiety'~~scanxiety' (~~39, 40~~41, 42)) and talked about their dependence on surveillance imaging to reassure them that the tumour had not recurred. The PPI group considered it important to determine whether surveillance imaging ~~at improving~~improved outcomes for CYP with medulloblastoma and ependymoma, but also to explore the experiences of those who have undergone surveillances as they considered that these may vary substantially.

This paper describes a protocol for the SCAN-ME study: a mixed-methods study evaluating the value of surveillance imaging for CYP with medulloblastoma and ependymoma. The study has the potential to impact families, clinicians, and decision makers by providing a holistic picture about the value of surveillance imaging~~-~~ within this population.

The qualitative workstream of this the SCAN-ME study will explore family's experiences of surveillance imaging following treatment for medulloblastoma and ependymoma. This will provide important insight into their perspective of scans and have the potential to impact future care and support for CYP and their parents in the period of follow-up care after treatment ends.

The efficacy of surveillance imaging for ependymoma and medulloblastoma remains uncertain, especially in the cases where prognosis after relapse is poor (~~10, 13~~14, 16). Difficulties in accurately measuring survival, owing to the impact of lead-time bias have made it more uncertain. The SCAN-ME study will ~~use two UK-based cohorts with~~utilise individual participant data to evaluate the effectiveness of surveillance imaging accurately by minimising the impact of lead-time bias. Not only this but the study will also evaluate the issue of length time bias by controlling for potential confounding variables. This will provide more clarity to decision makers as to whether surveillance imaging is effective ~~in~~ for medulloblastoma ~~or ependymoma~~, or whether it should only be utilised in particular subgroups.

Not only do decision makers need to consider the clinical effectiveness of surveillance imaging, but also whether surveillance imaging is value for money for healthcare reimbursement agencies. This will be addressed ~~in the SCAN-ME project workstreams~~ by comparing whether the additional costs associated with providing surveillance imaging is value for money compared to any improvements in clinical benefits and health-related quality of life. To our knowledge, this is the first economic analysis of surveillance imaging in this population.

The findings from the study will be discussed with stakeholders including clinicians and our PPI group, to ensure that the conclusions and implications to clinical practice are relevant. This is likely to be especially important in a situation where the results of the workstreams conflict – for example, if scans are found to not improve survival outcomes and is cost-ineffective but are deemed an important aspect of follow-up care to families of a child with medulloblastoma or ependymoma.