UNIVERSITY OF BIRMINGHAM

Study Protocol

FULL TITLE OF THE STUDY

Establish a comprehensive system to monitor the risks of adverse health and social outcomes among survivors of childhood, teenage and young adult cancer in Britain using two existing national population-based cohorts, the British Childhood Cancer Survivor Study (BCCSS) and the Teenage and Young Adult Cancer Survivor Study (TYACSS)

SHORT STUDY TITLE

Cancer Survivorship Studies

PROTOCOL VERSION NUMBER AND DATE

06 September 2025 version 5.0

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KEY STUDY CONTACTS

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Funder(s)	Children with Cancer UK World Cancer Research Fund CCLG: The Children & Young People's Cancer Association The Brain Tumour Charity
Key Protocol Contributors	Professor M M Hawkins and Dr Raoul Reulen – see above

STUDY SUMMARY

Study Title	Establish a comprehensive system to monitor the risks of adverse health and social outcomes among survivors of childhood, teenage and young adult cancer in Britain using two existing national population-based cohorts, the British Childhood Cancer Survivor Study (BCCSS) and the Teenage and Young Adult Cancer Survivor Study (TYACSS).
Internal ref. no. (or short title)	Cancer Survivorship Studies
Study Design	Individual patient record linkage of two population-based national cohorts (British Childhood Cancer Survivor Study (BCCSS) and the Teenage and Young Adult Cancer Survivor Study (TYACSS)) to several national registries/databases of adverse health and social outcomes.
Study Participants	Records relating to individuals who survived at least 5-years after diagnosis of childhood, teenage or young adult cancer in Britain.
Planned Size of Sample	BCCSS and TYACSS comprise 35,000 and 201,000 5-year survivors respectively.
Follow up duration	For life
Planned Study Period	5 years in the first instance
Research Question/Aim(s)	Undertake national population-based record linkage based investigations of the absolute and excess risks of: 1. Specific causes of death experienced by 5-year survivors of childhood, teenage, young adult and mature adult cancer, using the national death registries. 2. Subsequent primary cancers experienced by 5-year survivors of childhood, teenage, young adult and mature adult cancer, using the national death registries. 3. Hospitalisation for non-neoplastic conditions among 5-year survivors of childhood, teenage, young adult and mature adult cancer, using the national Hospital Episode Statistics database for England held by NHS England. 4. Cardiovascular conditions among 5-year survivors of childhood, teenage, young adult and mature adult cancer, using the National Institute of Cardiovascular Outcomes Research (NICOR) for England and Wales. 5. Receiving GP prescriptions for specific types of drugs among 5-year survivors of childhood, teenage, young adult and mature adult cancer, using the national NHS GP prescriptions database held by the National Cancer Registration and Analysis Service at NHS England. 6. The uptake of the full spectrum of mental health services available within the community among 5-year survivors of childhood, teenage, young adult and mature adult cancer using the national Mental Health Services Dataset held by NHS England. 7. The total burden of adverse health outcomes experienced by 5-year survivors of childhood, teenage, young adult and mature

	adult cancer by combining outcomes ascertained across all relevant record linkages. 8. Undertake national population-based investigations of the observed and expected levels of educational attainment among 5-year survivors of childhood, teenage and young adult cancer using the national data relating to educational attainment in schools, further education and higher education. 9. Undertake national population-based investigations of the observed and expected levels of employment among 5-year survivors of childhood, teenage, young adult and mature adult cancer using the national data relating to employment status of survivors. 10. Establish a cohort of offspring of survivors of cancer using recently developed methods which use the anonymised national Hospital Episode Statistics database. 11. Obtain improve measures of anti-cancer treatment received by survivors through linkage with the national BMT registry, relevant clinical trials, the national SACT chemotherapy dataset and the national radiotherapy dataset. 12. Identify individuals within the BCCSS who are also included in the West Midlands Regional Children's Tumour Registry (WMRCTR) to obtain detailed treatment information for investigations into adverse health outcomes relating to cumulative doses of cytotoxic agents and cumulative doses of radiation received.

FUNDING

FUNDER(S)	**QUANTITY**
Children with Cancer UK, for "Establish a comprehensive surveillance system for adverse health outcomes in British survivors of childhood, teenage and young adult cancer"	£350,000
World Cancer Research Fund, for "Effect of body composition, metabolic syndrome, physical activity, alcohol and smoking on long-term adverse health outcomes in survivors of childhood cancer"	£350,000
CCLG: The Children & Young People's Cancer Association, for "Establishment of a West Midlands Childhood Cancer Clinical Cohort"	£100,000
The Brain Tumour Charity, for "Establishment of a national system to monitor the risks of adverse health outcomes among the entire population of survivors of childhood, teenage and young adult brain tumour in Britain"	£300,000

ROLE OF UNIVERSITY AND FUNDER

Neither the University of Birmingham, nor any of the funders will have any influence on study design, study execution, data analysis and interpretation, manuscript writing or dissemination of the results.

ADVISORY GROUPS, PROJECT STEERING GROUP AND PPI

The study will be advised by both the Late Effects Group of the Children's Cancer and Leukaemia Group and the successor to the National Cancer Research Institute – Teenage and Young Adult & Germ Cell Tumour – Clinical Studies Group.

There will be a Project Steering Group for the research funded by The Brain Tumour Charity.

There is extensive Patient and Public Involvement (PPI) which is described in Section 5·4 on pages 19 to 20 below.

PROTOCOL CONTRIBUTORS

The protocol was developed by the University of Birmingham team i.e. Mike Hawkins (CI, Chair in Epidemiology and Director of the Centre for Childhood Cancer Survivor Studies); Raoul Reulen (Associate Professor); David Winter (Senior IT Manager); Jackie Hawkins (Research Support) in consultation with collaborators. Some initial feedback was sought from PPI representatives who are keen to be involved with the project and support dissemination of our results.

KEY WORDS: Cancer Survivorship Research
Adverse health outcomes in cancer survivors
Adverse social outcomes in cancer survivors
Risk stratification of cancer survivors
The British Childhood Cancer Survivor Study
The Teenage and Young Adult Cancer Survivor Study

STUDY FLOW CHART

Extend the existing BCCSS and TYACSS cohorts of survivors from the National Cancer Registries

The British Childhood Cancer Survivors Study (BCCSS) currently 35,000 5-year survivors of childhood cancer

The Teenage and Young Adult Cancer Survivor Study (TYACSS) currently 201,000 5-year survivors of teenage and young adult cancer

Individual patient electronic linkage to several national registries/databases of adverse health and social outcomes

Registry/Database	**Outcome ascertained**
National death registries	Cause of death
National cancer registries	Subsequent primary cancers
Hospital Episode Statistics database	Conditions resulting in hospitalisation
NHS database of GP prescriptions	Drugs and other interaction from GP
National Institute for Cardiovascular Outcomes Research (NICOR)	Cardiovascular diagnoses and procedures
The National Mental Health Services Dataset (MHSDS)	Consultations/interventions in the community concerning mental health
National educational attainment databases	School, Further Education, Higher Education outcomes
National employment databases	Employment status
West Midlands Regional Children's Tumour Registry (link with BCCSS only)	Potentially all above outcomes (initial focus on mental health and chronic pain)

Statistical analyses to compare risks of adverse outcomes among survivors with those expected from the general population

Such large-scale population-based investigations of the risks of a comprehensive spectrum of fatal and non-fatal adverse health and social outcomes provides the most reliable and unbiased evidence available for:

- feeding back to, counselling, educating and empowering survivors;
- developing evidence-based clinical follow-up guidelines;
- preparing "survivorship care plans";
- providing educational material for health care professionals including GPs;
- evaluating risks as well as benefits of proposals for future treatment protocols;
- advising national health authorities in relation to subgroups of survivors at particularly high risk for consideration of potential recall for counselling, surveillance or other intervention;
- identification of low risk groups for potential discharge from hospital based follow-up;
- provide risk stratification information to national health authorities, particularly NHS England, to guide the evidence-based levels of intensity of clinical follow-up needed by different specific subgroups of survivors;
- provide health economic evaluations from financial information recorded in hospital activity registers to compare the observed and expected costs relating to survivors.

RESEARCH PROPOSAL

Establish a comprehensive system to monitor the risks of adverse health and social outcomes among survivors of childhood, teenage and young adult cancer in Britain using two existing national population-based cohorts, the British Childhood Cancer Survivor Study (BCCSS) and the Teenage and Young Adult Cancer Survivor Study (TYACSS).

1. BACKGROUND AND RATIONALE

There is no comprehensive national system to monitor adverse health outcomes among the entire population of survivors of childhood, teenage and young adult cancer in Britain. However, there already exists two established national population-based cohorts of such survivors which would enable such a comprehensive monitoring system to be created. The British Childhood Cancer Survivor Study (BCCSS) includes 34,490 5-year survivors, Table 1. The Teenage and Young Adult Cancer Survivor Study (TYACSS) includes 200,945 5-year survivors, Table 2.

The aim would be to establish a system to monitor the risks of adverse health outcomes and related healthcare activity and cost among these survivors, and to determine how observed risks and costs compare with those expected from the general population to determine subgroups of survivors who experience substantially increased risk and who may place a higher demand on services.

Adverse health outcomes and associated costs would be obtained from electronic record linkage of the cohorts with existing national registries/databases.

The report by the Independent Cancer Taskforce “Achieving World-Class Cancer Outcomes – A Strategy for England 2015-2020” emphasised the importance of risk stratification of cancer survivors in relation to their risk of developing serious adverse health conditions to ensure that the intensity of clinical follow-up care is in proportion to such risk[1]. It is an unfortunate fact that individuals who have survived cancer experience greater risks of adverse health conditions[2], and greater risks of dying[3,4], than is expected from rates of these events in the general population. The national cancer strategies for Scotland[5] and Wales[6] also emphasise the importance of risk stratification of cancer survivors for proportionate clinical follow-up care.

The National Cancer Research Institute, NHS-England[7] and Public Health England[8] have historically each produced cancer strategies which also emphasise the importance of such risk stratification.

It is estimated that by 2030 there will be 4 million individuals living with the long-term consequences of cancer and its treatment, but unfortunately there is to date very little research on the problems which they experience, the causes and how they might be prevented or reduced in the future. The only exception to this general unsatisfactory situation relates to survivors of childhood cancer.

Recently there have been three UK-wide research priority setting initiatives involving detailed consultations with cancer patients/survivors, their families and friends, and health care professionals who treat or follow-up individuals who are living with or beyond cancer. Each of these research priority setting initiatives was overseen by the James Lind Alliance.

One initiative related to identifying research priorities relating to Teenagers or Young Adults with cancer at any stage in their cancer journey from diagnosis to long-term survival or death. Half of the final top 10 research priorities ultimately identified related to an issue concerning "cancer survivorship", that is concerns which relate to problems encountered after cancer treatment is completed and the survivor returns to 'normal' life. The 5 cancer survivorship research priorities identified which are addressed by our research proposal below are:

- What psychological support package improves psychological well-being, social functioning and mental health during and after treatment?

- What interventions, including self-care, can reduce or reverse adverse short and long-term effects of cancer treatment?

- What interventions are most effective in supporting young people when returning to education or work?
- What is the best method of follow-up and timing which causes the least psychological and physical harm, while ensuring relapse/complications are detected early?

- What targeted treatments are effective and have fewer short and long-term side-effects?

https://www.jla.nihr.ac.uk/priority-setting-partnerships/teenage-and-young-adult-cancer#tab-28621

Another research priority setting initiative was undertaken by the NCRI in collaboration with the James Lind Alliance and was concerned with individuals living with or beyond cancer, and was concerned with individuals diagnosed over the age of 16 years. A UK-wide survey obtained 1500 responses, of which 55% were patients/survivors and 45% were medical and nursing carers or other health related professionals. Seven of the top 10 research priorities which were selected are addressed by our research proposals below:

- What are the best models for delivering long-term cancer care including screening, diagnosing and managing long-term side effects and late-effects of cancer and its treatment (e.g. primary and secondary care, voluntary organisations, self-management, carer involvement, use of digital technology, etc.)?

- How can patients and carers be appropriately informed of cancer diagnosis, treatment, prognosis, long-term side-effects and late effects of treatments, and how does this affect their treatment choices?

- How can care be better co-ordinated for people living with and beyond cancer who have complex needs (with more than one health problem or receiving care from more than one specialty)?

- What are the short-term and long-term psychological impacts of cancer and its treatment and what are the most effective ways of supporting the psychological wellbeing of all people living with and beyond cancer, their carers and families?

- How can the short-term, long-term and late effects of cancer treatments be (a) prevented, and/or (b) best treated/ managed?

- What are the biological bases of side-effects of cancer treatment and how can a better understanding lead to improved ways to manage side-effects?

- How can we predict which people living with and beyond cancer will experience long-term side-effects (side-effects which last for years after treatment) and which people will experience late effects (side-effects which do not appear until years after treatment)?

https://www.jla.nihr.ac.uk/priority-setting-partnerships/living-with-and-beyond-cancer#tab-27506

The final of the three research priority setting initiatives related exclusively to identifying priorities for research relating to individuals living with or beyond a primary brain or spinal cord tumours. One of the top 10 research priorities that emerged was “What are the long-term effects (physical and cognitive) of surgery and/or radiotherapy when treating people with a brain or spinal cord tumour?”

http://www.jla.nihr.ac.uk/priority-setting-partnerships/neuro-oncology/downloads/Neuro-Oncology-Group-Final-Report-June-2015.pdf

The Cancer Survivorship Group (CSG) at the University of Birmingham was established in 1998. It is led by Professor Mike Hawkins, Director and Dr Raoul Reulen, Associate Professor. The British Childhood Cancer Survivor Study was initiated in 1998 and the Teenage and Young Adult Cancer Survivor Study about a decade later.

The British Childhood Cancer Survivor Study (BCCSS)

The BCCSS is underpinned by a national population-based cohort of 35,000 individuals who were diagnosed with cancer under the age of 15 years, between 1940 and 2006, in England, Wales or Scotland, and who survived at least 5 years from diagnosis. It has provided landmark insights into the risk of adverse health outcomes developing among childhood cancer survivors including the risk of specific causes of death in long-term survivors[3,4] , the risk of subsequent primary cancers,[10] and the risks of the total burden of adverse health outcomes experienced by different subgroups of survivors treated with therapies with varying levels of long-term toxicity[2]. There is serious premature morbidity and mortality experienced by survivors of cancer diagnosed when young. Among those diagnosed with childhood cancer in Britain our nationwide work indicates that by 50 years from diagnosis 30% of 5-year survivors have died when only 6% would be expected to have died from general population death rates[3]. Among mature survivors 50% and 25% of the excess number of deaths experienced were accounted for by subsequent primary cancers and cardiovascular disease, respectively[3]. Consequently providing insights into where strategies aimed at preventing premature mortality should be focused. Additionally, we were the first to demonstrate that survivors of childhood cancers who were treated with direct abdominal pelvic radiotherapy experience risks of bowel cancer similar to those experienced by individuals who have two first-degree relatives diagnosed with bowel cancer[10]. Increasingly clinicians are offering such survivors the option of a colonoscopy from a relatively young age because such options have been routinely offered to individuals with a strong family history of bowel cancer for many years. As part of the National Cancer Survivorship Initiative the then National Director for Cancer at the Department of Health (Professor Sir Mike Richards) requested that the BCCSS be used to produce a risk stratification tool relating to the entire British population of childhood cancer survivors for potential use in the NHS. The results of the work were published in November 2017 in the British Journal of Cancer and reported that the risk of a serious adverse health outcome by 45 years from diagnosis was 21%, 45% and 69% among those classified as being low, medium or high risk of experiencing toxicity based on their type of cancer and treatment combination that they received[2]. This evidence has recently been adopted by NHS England for use in hospitals throughout the NHS in the future for classifying every survivor of childhood, teenage and young adult cancer in relation to their long-term risk of developing a serious adverse health outcome and the corresponding intensity of clinical follow-up care which should be provided to them.

The Teenage and Young Adult Cancer Survivor Study (TYACSS)

The TYACSS was established using the national population-based cohort of 200,945 individuals diagnosed with cancer when aged 15 to 39 years inclusive, between 1971 and 2006, in England or Wales and who survived at least 5 years from diagnosis. Individuals diagnosed with cancer at these ages are internationally acknowledged as being under researched when compared with those diagnosed at younger or older ages. The TYACSS cohort is the largest such cohort in the world and the numbers available enable the production of reliable risk estimates; its population-based construction ensure avoidance of selection bias. In April 2019 we published in the Lancet Oncology the first large-scale study of the risks of new (subsequent primary) cancers developing in survivors of Teenage and Young Adult cancer[10]. An accompanying Commentary considered it a landmark contribution[11]. In particular because we identified a small number of specific new cancer types which accounted for most of the excess number of new cancers observed and therefore provided evidence useful to clinicians in focusing care when clinically following-up such survivors. Additionally we reported that lung cancer developed in excess of that expected among survivors of most specific TYA cancer, which is in contrast to the experience among survivors of childhood cancer. We have also published novel insights into the risks of stroke among survivors of TYA cancer and identified diagnostic groups at highest risk – again providing an evidence for focusing clinical follow-up care on those most at risk[12]. Also our nationwide work among TYA cancer survivors has demonstrated substantial excess mortality from cardiac[13] and respiratory disease.[14]

Uses of evidence produced for changing clinical practice and health policy

Such large-scale population-based investigations of the risks of a comprehensive spectrum of fatal and non-fatal adverse health outcomes has provided the most reliable and unbiased evidence available for:

- feeding back to, counselling, educating and empowering survivors;
- developing evidence-based clinical follow-up guidelines;
- preparing “survivorship care plans”;
- providing educational material for health care professionals including GPs;
- evaluating risks as well as benefits of proposals for future treatment protocols;
- advising national health authorities in relation to subgroups of survivors at particularly high risk for consideration of potential recall for counselling, surveillance or other intervention;
- identification of low risk groups for potential discharge from hospital based follow-up;
- provide risk stratification information to national health authorities, particularly NHS England, to guide the evidence-based levels of intensity of clinical follow-up needed by different specific subgroups of survivors;
- provide health economic evaluations from financial information recorded in hospital activity registers to compare the observed and expected costs relating to survivors.

Proven impact of our previous publications

The evidence which we have previously produced has had impact in a number of policy and clinical practice areas:

- The comprehensive risk stratification evidence produced already in relation to survivors of childhood, teenage and young adult cancer concerning their risk of serious adverse health outcomes in relation to their type of cancer, type of cancer treatment received, treatment era, age at treatment, years from cancer diagnosis, attained age and gender has had impact. Our initial publication concerned with the long-term risk of the total burden of serious adverse health outcomes carried out as part of the National Cancer Survivorship Initiative, identified subgroups of survivors a high, medium and low risk. This publication has recently been used as key evidence in review which NHS England

has undertaken of its Service Specifications. In the future every survivor of childhood, teenage or young adult cancer will be assessed in relation to their long-term risk of developing serious adverse health outcomes using our risk stratification tool at the end of treatment and this will inform clinical decisions regarding the intensity of clinical follow-up necessary ranging from survivor self-management with easy and rapid access back into the NHS system at one end, to regular hospital consultant led multi-disciplinary team care at the other.

https://www.engage.england.nhs.uk/consultation/childrens-cancer-services/user_uploads/service-specification-childrens-networks-and-principle-treatment-centres.pdf

https://www.engage.england.nhs.uk/consultation/teenager-and-young-adults-cancer-services/user_uploads/service-specification-tya-principal-treatment-centres-and-networks.pdf

- The recently established International Late Effects of Childhood Cancer Guideline Harmonization Group (www.ighg.org) led by key European and US investigators aims to produce standard clinical follow-up guidelines for survivors which are as evidence-based as possible and acceptable to clinical communities throughout the world. Professor Mike Hawkins and Dr Raoul Reulen have been closely involved in this initiative and in particular in the development of several recent and on-going international guidelines.

- Advising national health authorities of subgroups of survivors with particularly high risks of specific outcomes for potential recall or other intervention. There is on-going work concerning the introduction of screening (colonoscopy/faecal occult blood sampling) for bowel cancer in survivors of childhood cancer who received external beam radiotherapy to the abdominopelvic region; also on-going work into understanding whether there are any ways to reduce the substantial risks of stroke in survivors of childhood, teenage and young adult cancer who received external beam radiotherapy for an intracranial tumour.

- Professor Mike Hawkins and Dr Raoul Reulen regularly speak at the Annual Education Day organised by the Late Effects Group of the Children's Cancer and Leukaemia Group. This is well attended (100 to 150 attendees) by those responsible for the care (doctors and nurses) of survivors of childhood cancer at Centres throughout the UK.

- Professor Mike Hawkins and Dr Raoul Reulen are full members of both the Children & Young People's Cancer Association (CCLG) and the Late Effects Group of the CCLG.

- The BCCSS receives formal clinical input into its research plans from a CCLG/BCCSS liaison/advisory committee jointly organised by the Late Effects Group of the CCLG and the Cancer Survivorship Group.

- The TYACSS receives formal clinical input into its research plans from the successor to the NCRI-TYA&GCT-Group of which Professor Mike Hawkins and Dr Raoul Reulen are both full members.

Three serious limitations of previous research relating to British survivors of cancer diagnosed when young relate to the absence of national databases relating to cardiovascular conditions, GP prescriptions and the use of mental health facilities accessed within a community setting – each of these limitations can now be overcome with the current proposal.

There has been very little previous research concerned with the healthcare costs relating to British survivors of cancer diagnosed when young and how these compare with those expected from the general population. This can now be addressed for England and Scotland because the data and expertise will be available to the project.

2. THEORETICAL FRAMEWORK – ADVANTAGES OF LARGE-SCALE POPULATION-BASED COHORTS

The considerable advantages of large-scale cohorts, particularly when population-based, to understand the risks and causes of adverse health outcomes developing in survivors of cancer has been previously provided.[15] Firstly it is important to distinguish epidemiological follow-up of survivors from clinical follow-up. The former should provide the evidence to underpin the latter. Here we are concerned with providing systematic and comprehensive epidemiological follow-up.

Large-scale population-based cohorts have considerable advantages over the alternatives which comprise single centre or multi-centre hospital-based studies or following-up groups of individuals treated within a single or multiple clinical trials. Hospital based studies are inevitably much smaller than large-scale population-based cohorts and have insufficient numbers to satisfactorily investigate all but the most commonly occurring adverse health outcomes. Also there is a problem with patients becoming lost to hospital follow-up and if this becomes a substantial fraction of the entire hospital population there are inevitably concerns relating to how representative of the entire population are those that remain.

Clinical trials overwhelmingly address questions of treatment efficacy and the maximum follow-up period tends to be between 5 and 10 years. Some adverse health effects of cancer or its treatment take decades to emerge. Clinical trials have exclusion criteria which result in generally more healthy patients being included because they are robust enough to withstand the treatments. Also the treatments used in clinical trials tend to be very homogeneous, except for the efficacy question, compared to the heterogeneity of treatment occurring across the whole population. The latter heterogeneity is critically important for this investigation of dose-response across a comprehensive range of factors. The proportion of individuals with cancer who are entered into clinical trials rarely exceeds 50%, even for childhood cancer for whom entry into trials is highest only for a very small number of cancer types do more than 50% get entered into trials. The advantages of large-scale population-based cohorts are multiple: large-scale ensures greater numbers to detect rarer risks; population-based ensuring heterogeneity in treatment available and avoidance of selection bias; provides the option to study any outcome; nested case-control studies provide one of the most cost-effective ways to investigate risk factors, including aspects of treatment, in detail.

Britain has particular advantages for establishing cancer survivor cohorts compared with most other countries in the world because of the long-standing existence of nationwide population-based cancer registration which began in the early 1960s. As a consequence cancer survivor cohorts benefit from some of the longest follow-up periods currently available to any such cohort worldwide.

We shall undertake individual patient electronic record linkage between each of the BCCSS and TYACSS cohorts and several national outcome registers/databases including:

- national causes of death registry in England, Scotland and Wales
- national cancer registry in England, Scotland and Wales
- national Hospital Episode Statistics data for England
- National Institute of Cardiovascular Outcomes Research for England and Wales
- national NHS GP prescription database maintained by NHS England
- national Mental Health Services Dataset
- national educational outcomes database
- national employment status database.
- West Midlands Regional Children's Tumour Registry (WMRCTG)

To improve our measures of exposure to anti-cancer treatment among survivors we shall also undertake individual patient electronic record linkage with the national BMT registry, relevant clinical trials, the national SACT chemotherapy dataset and the national radiotherapy dataset.

We shall exploit the advantages which Britain has compared with other parts of the world, with the exception of the Nordic countries, because of the long-standing existence of nationwide population-based cancer registration. We have established the two largest population-based cohorts available relating to childhood cancer survivors and teenage and young adult cancer survivors – the BCCSS and TYACSS, respectively. These cohorts benefit from the longest follow-up time currently available to any similar cohorts as a result of national population-based cancer registration being established in Britain in the early 1960s.

We shall extend as specified above the electronic record linkage between each of the BCCSS and TYACSS cohorts and: the national death and cancer registries, the national hospitalisation databases, the national cardiovascular databases, the national GP prescription databases and the national community mental health services databases. This will provide ascertainment of all: deaths with details of underlying cause; subsequent primary neoplasms diagnosed; outpatient, inpatient and emergency care episodes at NHS hospitals; cardiovascular events and procedures, GP prescriptions dispensed to survivors; mental health services used within the community. Linkage to national databases relating to educational attainment and employment status will be undertaken.

In addition, we shall provide NHS England with identifiers to identify individuals within the BCCSS who have been diagnosed with cancer in the West Midlands and are also included in the West Midlands Regional Children's Tumour Registry to ascertain the full spectrum of adverse health outcomes through linkage.

3. RESEARCH QUESTION/AIM(S)

Undertake national population-based record linkage based investigations of the absolute and excess risks of:

1. Specific causes of death experienced by 5-year survivors of childhood, teenage, young adult and mature adult cancer, using the national death registries.

2. Subsequent primary cancers experienced by 5-year survivors of childhood, teenage, young adult and mature adult cancer, using the national death registries.

3. Hospitalisation for non-neoplastic conditions among 5-year survivors of childhood, teenage, young adult and mature adult cancer, using the national Hospital Episode Statistics database for England held by NHS England.

4. Cardiovascular conditions among 5-year survivors of childhood, teenage, young adult and mature adult cancer, using the National Institute of Cardiovascular Outcomes Research (NICOR) for England and Wales.

5. Receiving GP prescriptions for specific types of drugs among 5-year survivors of childhood, teenage, young adult and mature adult cancer, using the national NHS GP prescriptions database held by the National Cancer Registration and Analysis Service at NHS England.

6. The uptake of the full spectrum of mental health services available within the community among 5-year survivors of childhood, teenage, young adult and mature adult cancer using the national Mental Health Services Dataset held by NHS England.

7. The total burden of adverse health outcomes experienced by 5-year survivors of childhood, teenage, young adult and mature adult cancer by combining outcomes ascertained across all relevant record linkages.

8. Undertake national population-based investigations of the observed and expected levels of educational attainment among 5-year survivors of childhood, teenage and young adult cancer using the national data relating to educational attainment in schools, further education and higher education.

9. Undertake national population-based investigations of the observed and expected levels of employment among 5-year survivors of childhood, teenage, young adult and mature adult cancer using the national data relating to employment status of survivors.

10. Establish a cohort of offspring of survivors of cancer using recently developed methods which use the anonymised national Hospital Episode Statistics database.

11. Obtain improve measures of anti-cancer treatment received by survivors through linkage with the national BMT registry, relevant clinical trials data, the national SACT chemotherapy dataset and the national radiotherapy dataset.

12. Identify individuals within the BCCSS who are also included in the West Midlands Regional Children's Tumour Registry (WMRCTR). The WMRCTR holds more detailed treatment information than the BCCSS allowing us to investigate adverse health outcomes relating to cumulative doses of cytotoxic agents and cumulative doses of radiation received among those included in the WMRCTR.

4. METHODOLOGY

4.1 British Childhood Cancer Survivor Study (BCCSS)

4.1.1 Ascertainment and validation of adverse health or social outcomes for the BCCSS

The BCCSS has been electronically linked to the national death and cancer registries for England, Wales and Scotland; also to the national Hospital Episode Statistics database for England. These linkages would need to be updated to ascertain events in more recent years since previous linkage. Linkage with the relevant registries maintained by the National Institute of Cardiovascular Outcomes Research (NICOR) will need to be undertaken from the beginning. Linkage with the national NHS database of general practitioner prescriptions has been initiated with NHS England through the award of a PhD studentship funded by NHS England and supervised by Professor Hawkins

and Dr Reulen together with Dr Katherine Henson at NHS England. Professor Hawkins and Dr Reulen each hold an honorary contract with NHS England. Linkage with the Mental Health Services Dataset will need to be undertaken afresh, but detailed discussions have already taken place to establish its feasibility and we can provide a letter of support from NHS England indicating their full support. Discussions have taken place with the Department for Education (England) concerning linkage to educational attainment in schools, further education and higher education, again we can provide emails indicating full support from the Department of Education. Discussion with the Department for Work and Pensions is on-going concerning linkages to employment status of survivors.

Validation of potential subsequent primary cancers ascertained through linkage with the national cancer registry will be achieved through three complementary approaches. Inspection of relevant national Hospital Episode Statistics database records; writing to GPs as 'gatekeepers' for confirmatory evidence with the survivors' consent; writing to pathologists when GPs do not have sufficient information.

In addition, we shall extend the BCCSS cohort with more recently diagnosed individuals as the most recent year currently included is 2006. We currently have CAG permission to link the BCCSS with the *West Midlands Regional Children's Tumour Registry* (WMRCTR*),* however, to identify those new patients who are included both in the BCCSS and the WMRCTR we need to provide NHS England with identifiers (NHS number, sex, date of birth, full name) so that NHS England can identify those individuals in the updated dataset. We have been in discussion with NHS England over the last few months and they are very supportive of our plans and agreed in principle to provide the relevant data. We are in the process of agreeing a formal Data Sharing Agreement, but for this we need CAG approval for the work. To obtain more detailed information on potential treatment, we will link the BCCSS with national childhood cancer trials data, including historical trials data on leukaemia patients currently held at the University of Newcastle (Prof Anthony Moorman).

4.1.2 BCCSS – risk factors to be investigated

We shall investigate variation in the absolute and excess risks of specific adverse health outcomes, and the total burden of all adverse health outcomes combined, across the different levels of the following factors: type of cancer, site of cancer, type of anti-cancer treatment received, treatment era, age at diagnosis, years from diagnosis, attained age and gender.

4.2 Teenage and Young Adult Cancer Survivor Study (TYACSS)

4.2.1 Ascertainment and validation of adverse health and social outcomes for the TYACSS

The TYACSS cohort has already been electronically linked to the national death and cancer registries for England and Wales; also to the national Hospital Episode Statistics database for England. Linkage with regard to other outcomes is in a similar situation as described for the BCCSS above. Linkages will be regularly updated top ensure that events are ascertained as up-to-date as possible.

There will be no validation of potential subsequent primary cancers within the TYACSS cohort as there are far too many events for it to be feasible. Instead

we shall use internationally agreed systems for the identification of subsequent primary cancers from cancer registration data.

4.2.2 TYACSS – risk factors to be investigated

We shall investigate variation in the absolute and excess risks of specific adverse health outcomes across levels of the following factors: type and site of cancer, treatment era, age at diagnosis of cancer, years from cancer diagnosis, attained age and gender. There is no treatment information available. However, in marked contrast to survivors of childhood cancer there is very little published based on large-scale population-based data concerning variation in the risks of adverse health outcomes in relation to any risk factors among survivors of teenage and young adult cancer. Therefore we anticipate that this work will provide an important contribution in an area with little existing knowledge. Our recent contribution concerning subsequent primary neoplasms was internationally regarded as a landmark contribution.[11]

4.3 Statistical analyses:

4.3.1 Risks of specific causes of death

Each individual enters risk at the date of 5-year survival and contributes person-years until the exit date (first of emigration date or date of end of ascertainment). Standardised Mortality Ratios (SMRs) and Absolute Excess Risks (AERs) will be calculated as O/E and [(O-E)/py]*10000 where O and E are the observed and expected numbers of deaths, respectively, and 'py' is the person-years at risk accumulated. To investigate variation in SMRs and AERs across levels of risk stratification factors Poisson regression models will be utilised as in our previous work.[3,4] The cumulative incidence of death from a specific cause will be estimated treating other causes of death as competing risks.[3,4]

4.3.2 Risks of subsequent primary neoplasms (SPNs)

Similar statistical methodology to that described for deaths would be used to determine subgroups of survivors at substantially excess risk of specific SPNs, but the summary measures would be Standardised Incidence Ratios (SIRs) and Absolute Excess Risks (AERs defined as for deaths, in terms of observed (O) and expected (E) numbers of SPNs of a particular site/type, as in our previous work.[9,10]

4.3.3 Risk of non-neoplastic adverse health outcomes including hospitalisation, cardiovascular events, GP prescriptions, use of community mental health facilities, educational attainment and employment status

The period at risk begins from the start date for ascertainment of the specific outcome and ends at the current end date of ascertainment provided the survivor does not exit through emigration or death before this end date. Two types of analysis would be undertaken:

a) Internal analyses

The risk of a specific adverse health outcome would be compared over the period at risk using Poisson regression in relation to the risk stratification factors. In this way it would be possible to identify particular subgroups at greatest risk.

b) External analyses

We will have the general population hospitalisation, GP prescription and community mental health events classified by age, sex and calendar year. By dividing the number of events in each cell by the general population estimate of those at risk provides an expected rate for the derivation of expected numbers. Again Poisson regression would be used to compare the observed and expected numbers over the levels of a particular risk factor adjusting for others.

We have previously used these approaches successfully.[12,16]

4.3.4 Cost analysis

Unit costs will be assigned to healthcare activity using standard Department of Health (DoH) and Scottish Government guidance. Healthcare Resource Group (HRG) codes will be assigned to secondary care episodes using the DoH Grouper software with sensitivity analysis between year-specific and common-base-year assignment. Prescriptions will be costed using the national tariff for branded medicines and the electronic medicines compendium for generic medicines. Scottish cost assignment will rely on the Scottish Cost Book and 'paid activity' that relies on dispensing records in addition to expected prescription costs. On this basis, the cost of subsequent primary neoplasms, the cost of non-neoplastic adverse events and the overall cost-profile of survivors will be described.

Comparison of overall costs and cost profiles will be made descriptively through cost-profile visualisation. In parallel with the risk analysis described above, internal analysis will identify predictors of cost using generalised linear models. External analysis based on the same cells as the risk analysis will estimate observed and expected cost compared with the general population.

5. ETHICAL AND REGULATORY CONSIDERATIONS INCLUDING CONSENT

5.1 Assessment and management of risk

The work proposed concerns entirely national database studies using individual patient electronic record linkage to link individuals within the BCCSS and TYACSS cohorts to several national registries or databases of adverse health and social outcomes. There is no direct contact with the individuals involved and so there is very little potential for the risk of harm to study participants, their family and friends.

5.2 Research Ethics Committee (REC) and other regulatory review

Before the start of the study a favourable opinion will be sought from a regional research ethics committee established by the NHS Health Research Authority (NHS-REC).

In the future should the need arise for a substantial amendment then this would be submitted to the NHS-REC to seek a favourable opinion before implementation.

In the past we have sought and obtained Section 251 support from the Confidential Advisory Group (CAG) to undertake linkages of the databases of cancer survivors (the BCCSS and TYACSS cohorts currently include 35,000 and 201,000 individual 5-year survivors, respectively) with the national registries/databases of adverse health and social outcomes which are suspected to affect cancer survivors to a substantially greater extent than expected from members of the general population

of similar age and gender. Increasingly new national electronic adverse health and social outcome registries/databases are becoming available enabling a more comprehensive understanding of the increased risks of such outcomes experienced by cancer survivors. Before the start of the study a favourable opinion would be sought from CAG to undertake the linkages with Section 251 support.

5.3 Peer review

All of the research proposed has been the subject of international peer-review undertaken independently by the cancer charities who fund our research (including Children with Cancer – UK, the Dutch Cancer Society, and The Brain Tumour Charity). Additionally Public Health England (now NHS England) undertook independent peer-reviewing of the aspects of research which they are funding.

5.4 Patient and Public Involvement

5.4.1 Research Priority Setting Partnership overseen by the James Lind Alliance

As reported above in section '1. Background and Rationale' the research proposed here has been identified as being among the top-ten research priorities in three Research Priority Setting Partnership initiatives overseen by the James Lind Alliance. Survivors are central to identifying such research priorities in James Lind Alliance led initiatives.

5.4.2 Questionnaires returned by 10,500 survivors of childhood cancer living throughout Britain

As part of a previous funding period a postal questionnaire concerned with adverse health and social outcomes was sent to every survivor of childhood cancer in Britain aged at least 16 years, 15,000 individuals, and 10,500 (70%) returned a completed questionnaire. This is a very high response for a postal questionnaire survey and indicates the importance with which the survivors regarded the survey. Additionally, 93% gave their consent for validation of the medical conditions reported in questionnaires using medical records; 95% gave their consent for their information to be kept permanently. All of this indicates the importance with which the research proposed is regarded by those involved.

5.4.3. Specific PPI group established for research funded by The Brain Tumour Charity

In the development of our successful grant application to The Brain Tumour Charity we consulted with their Research Involvement Network (RIN) which is comprised exclusively of survivors of a brain tumour. Twelve members of the RIN fed-back in detail on research proposals and this impacted the research. We have agreed that two members of the RIN will join the Project Steering Group and therefore have influence over the entire lifetime of the project.

5.4.4 Local group of survivors of childhood cancer

Dr Helen Jenkinson, Consultant Paediatric Oncologist at the Birmingham Children's Hospital has established a local group of about 20 survivors to be consulted on both clinical and research questions. Dr Jenkinson has indicated that this group may be asked to provide guidance to the survivorship research relating to survivors of childhood cancer.

5.4.5 Birmingham Cancer Research UK Centre PPI Group

There is a Cancer Research UK funded Senior Research Nurse at the Birmingham Cancer Research UK Centre who maintains a group of about 20 survivors of a variety of cancer diagnosed at a range of adult ages. We have consulted with, and will continue to consult with, this group of survivors.

5.4.6 Pancare https://www.pancare.eu/mission-and-vision/

Professor Hawkins is a founding member of PanCare an organisation for: childhood cancer survivors and their families; clinicians caring for those with, or cured of, cancer; researchers addressing the needs of those with, or cured of childhood cancer. This pan-European organisation meets twice each year and has a significant survivor membership. This provides an international forum to seek input from survivors into research being undertaken or planned.

5.4.7 The successor to National Cancer Research Institute – Teenage and Young Adult & Germ Cell Tumour – Clinical Studies Group (NCRI-TYA&GCT-CSG)

Professor Hawkins and Dr Raoul Reulen are both full members of this national group and there are also two survivors of TYA cancer among the membership. This provides a national forum for input from survivors into survivorship research studies.

5.5 Protocol compliance

Protocol compliance will be monitored via fortnightly meetings of the research team. The work to be undertaken involves a small number of individuals and protocol compliance has never been a problem in the past 20 years during which this research has been active under the Directorship of Professor Hawkins at the University of Birmingham.

5.6 Data protection and patient confidentiality

All investigators and study staff have annual refresher testing in relation to data protection and patient confidentiality as this is a requirement of the University of Birmingham. Professor Hawkins is Chair of the Committee for Research Governance and Data Protection within the whole of the Institute of Applied Health Research at the University of Birmingham and all researchers associated with this project are members of this Committee. We are all aware of the requirements of the General Data Protection Regulation and the Data Protection Act 2018 and take them very seriously.

- Personal information is stored separate from other data relating to individuals. The personal information is not accessible to anyone via the internet.
- In analysis files personal information is replaced by a random number.
- There is secure maintenance of linking information in separate locations using encrypted digital files which are password protected.
- The identified data is accessible to the Data Manager only. A small number of specified researchers in Birmingham have access to the non-identified data for analysis.

- Only aggregated data is shared with co-investigators.

- The data is stored for the period for which there is consent to store it.

5.7 Indemnity

The University of Birmingham is the sponsor of the research and has insurance to cover potential legal liability relating to harm to study participants from the execution of the research.

5.8 Access to the final study dataset

- Only members of the research team in Birmingham will have access to the final full dataset.

- Should the opportunity arise to undertake related research using these national cohorts as a national resource and starting point then a separate NHS-REC application will be made in relation to that research.

6. DISSEMINATION POLICY

- Manuscripts will be prepared for publication in international peer-reviewed journals. There are already over 70 such manuscripts published using the BCCSS cohort, and about 5 published using the TYACSS cohort.

- Funding bodies will need to be acknowledged within peer-reviewed publications but they have no rights to alter, delay or prevent such publications.

- We intend to establish a website for the study which will contain information regarding progress, accessible summaries of the research in the form of regular newsletters.

- We have been approached by specific members of the BCCSS cohort in the past to request medical records we may hold relating to treatment for a specific cancer as these have been lost by the NHS. This has been critically important on several occasions in avoiding the risk of serious complications to a major organ through appropriate restriction of the cumulative life-time dose of radiation from radiotherapy.

- The Study Protocol, a complete list of publications and Newsletters will be available on the Study Website.

- Authorship eligibility will be determined to be consistent with the requirements of the leading international general medical journal including New England Journal of Medicine, The Lancet, the Journal of the American Medical Association and the British Medical Journal.

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TABLE 1 Structure of British Childhood Cancer Survivor Study (BCCSS)

The British Childhood Cancer Survivor Study cohort which originally comprised 17,980 individuals diagnosed with childhood cancer, in Britain, between 1940 and 1991 and who survived at least 5 years. The cohort has now been extended to include the corresponding 16,509 5 year survivors diagnosed between 1992 and 2006. The numbers of different cancers included within the original and extended cohorts are provided below.

First Primary Neoplasm Type		1940-1991	1992-2006	Total
Leukaemia	Count	4,852	5,622	10,474
	Row %	46.3%	53.7%	100%
	Column %	27.0%	34.1%	30.4%
Hodgkin Lymphoma	Count	1,326	908	2,234
	Row %	59.4%	40.6%	100%
	Column %	7.4%	5.5%	6.5%
Non Hodgkin Lymphoma	Count	878	671	1,549
	Row %	56.7%	43.3%	100%
	Column %	4.9%	4.1%	4.5%
CNS tumours	Count	4,210	3,958	8,168
	Row %	51.5%	48.5%	100%
	Column %	23.4%	24.0%	23.7%
Neuroblastoma	Count	766	769	1,535
	Row %	49.9%	50.1%	100%
	Column %	4.3%	4.7%	4.5%
Non-heritable Retinoblastoma	Count	648	358	1,006
	Row %	64.4%	35.6%	100%
	Column %	3.6%	2.2%	2.9%
Heritable Retinoblastoma	Count	552	198	750
	Row %	73.6%	26.4%	100%
	Column %	3.1%	1.2%	2.2%
Wilms tumour	Count	1,441	947	2,388
	Row %	60.3%	39.7%	100%
	Column %	8.0%	5.7%	6.9%
Bone Sarcoma	Count	664	531	1,195
	Row %	55.6%	44.4%	100%
	Column %	3.7%	3.2%	3.5%
Soft Tissue Sarcoma	Count	1,181	966	2,147
	Row %	55.0%	45.0%	100%
	Column %	6.6%	5.9%	6.2%
Other	Count	1,462	1,581	3,043
	Row %	48.0%	52.0%	100%
	Column %	8.1%	9.6%	8.8%
Total	Count	17,980	16,509	34,489
	Row %	52.1%	47.9%	100%
	Column %	100%	100%	100%

TABLE 2 Structure of the Teenage and Young Adult Cancer Survivor Study (TYACSS)

The Teenage and Young Adult Cancer Survivor Study population-based cohort comprises 200,945 individuals diagnosed with cancer when aged 15 to 30 years in England & Wales, between 1971 and 2006 and who survived at least 5 years. The numbers of different cancers included within this cohort are provided below.

First Primary Neoplasm Type	N	%
Breast	36,236	18.0%
Testicular	24,309	12.1%
Cervix	23,281	11.6%
Melanoma	22,446	11.2%
CNS	17,280	8.6%
Hodgkin Lymphoma	16,971	8.5%
Non-Hodgkin Lymphoma	9,467	4.7%
Thyroid	7,809	3.9%
Gastrointestinal	7,224	3.6%
Soft Tissue Sarcoma	6,130	3.1%
Ovary	4,885	2.4%
Bladder	4,685	2.3%
Other Genitourinary	4,672	2.3%
Head & Neck	3,961	2.0%
Leukaemia	5,073	2.6%
Bone Tumour	2,241	1.1%
Lung	1,219	0.6%
Other	3,056	1.5%
Total	200,945	100